(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 February 2002 (14.02.2002)

PCT

(10) International Publication Number
WO 02/12196 A2

(51) International Patent Classification[7]: C07D 223/00

(21) International Application Number: PCT/US01/22829

(22) International Filing Date: 20 July 2001 (20.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/633,751 7 August 2000 (07.08.2000) US

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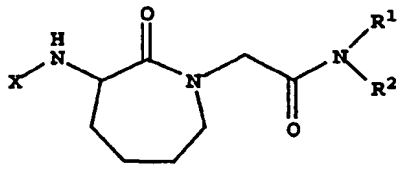
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

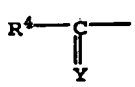
Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

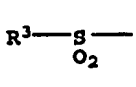
(54) Title: LACTAM COMPOUNDS AND THEIR USE AS INHIBITORS OF SERINE PROTEASES AND METHOD



(I)



(a)



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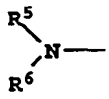

(i)

(ii)

(57) Abstract: Lactam inhibitors are provided which have the structure (I), x is (a) or (b) wherein Y is O or S and R^4 is (i), (ii) or R^8 at least one of R^1 and R^2 is hydrogen, and R^1, R^2, R^3, R^5, R^6, R^7, and R^8, are as defined herein. These compounds are inhibitors of tryptase and thus are useful in treating asthma. Methods for treating asthma and related diseases are also provided.

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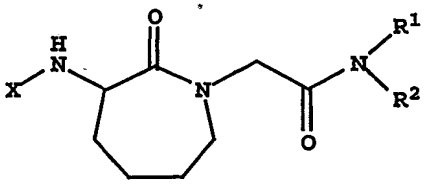
LACTAM COMPOUNDS AND THEIR USE AS INHIBITORS OF SERINE PROTEASES AND METHOD

The present invention relates to lactam inhibitors of tryptase, which are useful as anti-inflammatory agents particularly in the treatment of chronic asthma and related diseases.

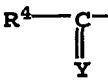
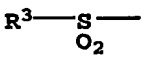
In accordance with the present invention, novel substituted lactam derivatives are provided which are inhibitors of serine proteases and have the structure I

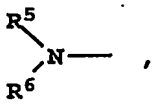
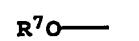
I.



including pharmaceutically acceptable salts thereof and all stereoisomers thereof, and prodrug esters thereof, wherein at least one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aminoalkylaryl, aminocycloalkylalkyl, aminoalkyl, aminoalkylcycloalkyl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro,

cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, aminoalkyl, alkyloxycarbonylaminoalkyl, arylalkyloxycarbonylaminoalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl;

X is  or 

Y is O or S and R^4 is  ,  or R^8

R^3 is selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, or polycycloalkenylalkyl; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl,

aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl;

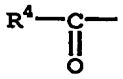
R^5 and R^6 are the same or different and are independently selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, arylcarbonyl, alkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, arylsulfonyl, or alkylsulfonyl, or R^5 and R^6 can be taken with the nitrogen to which they are attached to form a cycloheteroalkyl ring; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl;

R^7 and R^8 can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenyl-alkyl, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl.

In preferred embodiments, where in the formula I compounds

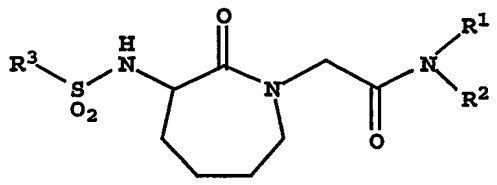
X is  or

and (1) R^1 and R^2 are independently alkyl, cycloalkyl, alkenyl, phenyl, benzyl, cyanoalkyl, alkoxycarbonylalkyl, or phenyl mono- or disubstituted with lower alkyl, cyano, hydroxy, dialkylamino, alkoxy, benzyloxy, alkylamino, alkoxycarbonyl, pyrrolidino, morpholino, halogen, alkyl substituted with one or more fluorines, then Y is S;

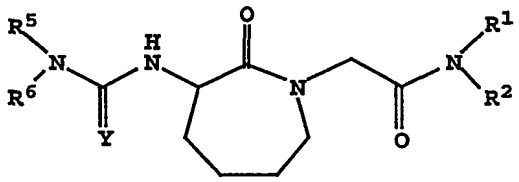
and (2) where X is  and R^4 is R^8, then R^8 is other than alkyl substituted with hydroxyaminocarbonyl.

Thus, the compounds of formula I of the invention can have the following structural formulae:

IA



IB



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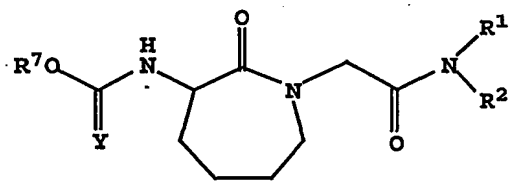
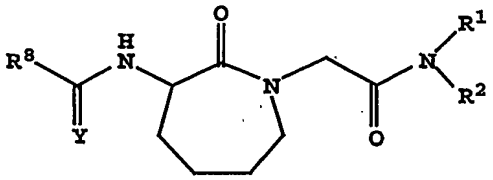
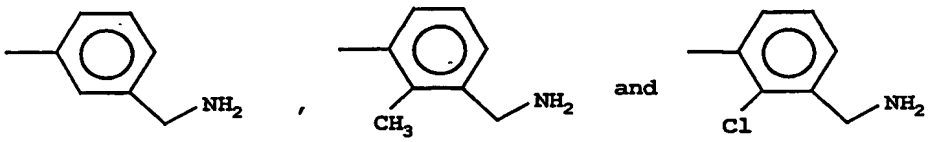


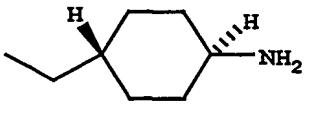
ID



Preferred are compounds of formula ID wherein one of R^1 and R^2 is hydrogen and Y is O.

More preferred are compounds of formula ID wherein R^1 is H and R^2 is aminoalkylaryl such as



and aminocycloalkylalkyl, such as  , and y is O.

Preferred compounds of the invention have the structures

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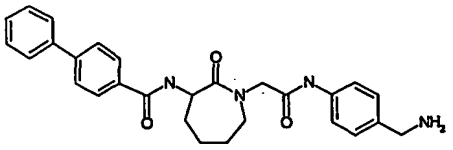
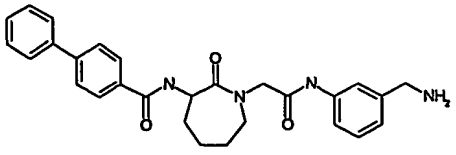
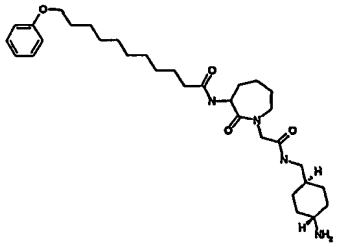
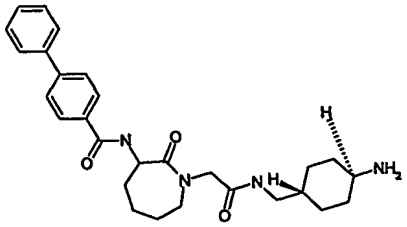
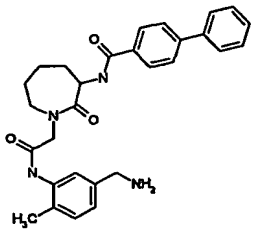
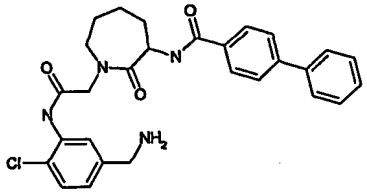


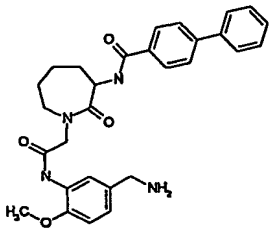


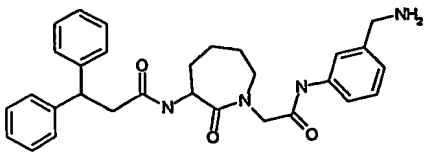


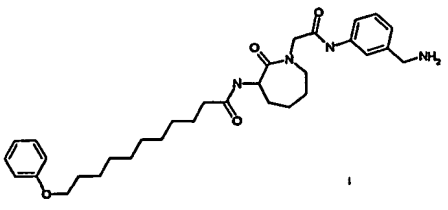


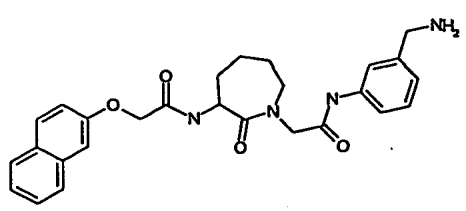


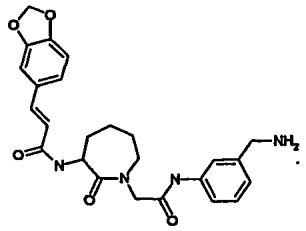


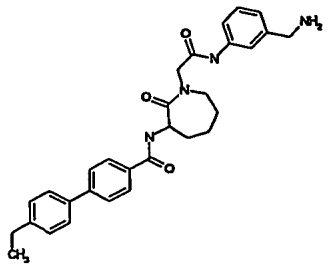


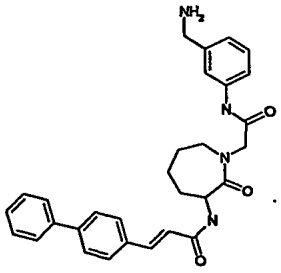


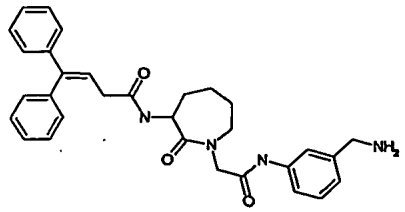


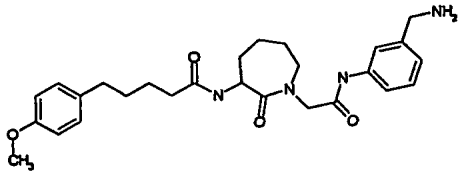


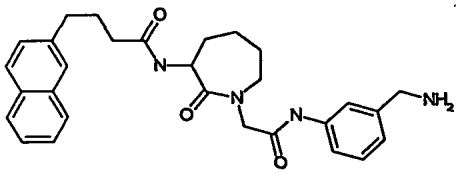


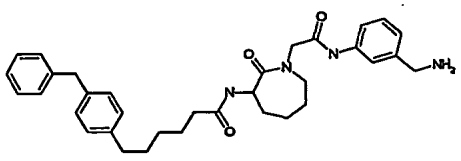


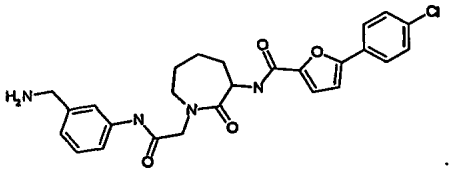


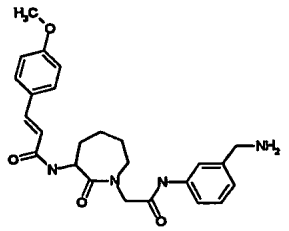


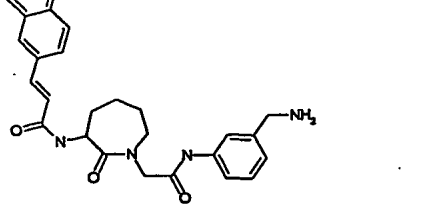


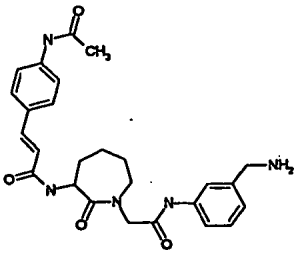


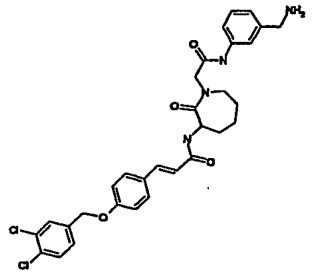


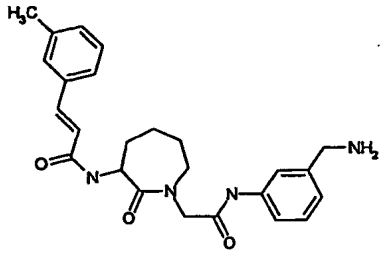


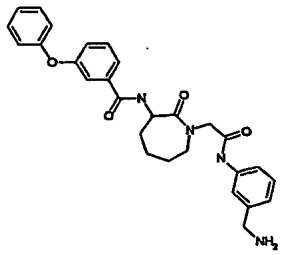


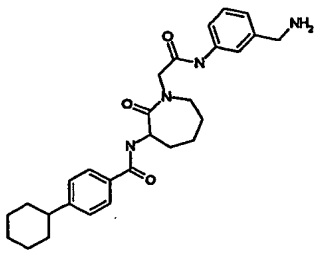


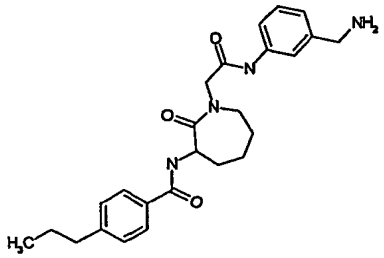


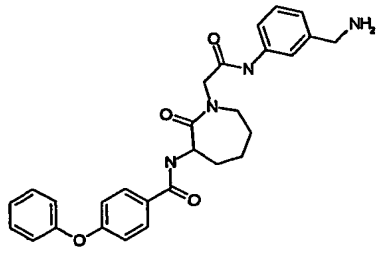


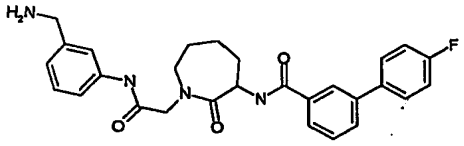


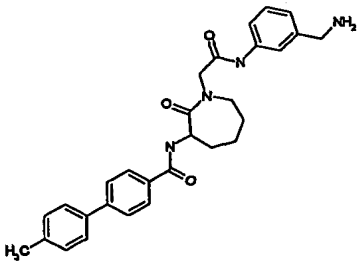


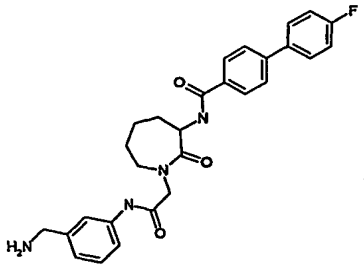


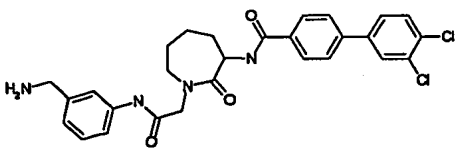












It will be appreciated that in compounds illustrated above and throughout, where a nitrogen is included with an apparent open valence, the nitrogen includes a hydrogen atom.

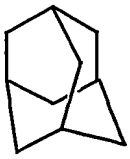
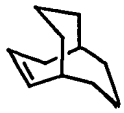
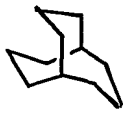
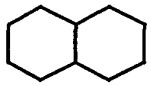
In addition, in accordance with the present invention, a method for treating and/or preventing medical conditions related to tryptase (such as asthma, chronic asthma or allergic rhinitis) is provided, wherein a compound of formula I is administered in a therapeutically effective amount which inhibits tryptase.

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons (in the case of alkyl or alk), preferably 1 to 20 carbons, more preferably 1 to 12 carbons (in the case of lower alkyl), in the normal chain,such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various additional branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents which may be any of the R^1 or the R^1 substituents set out herein.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 12 carbons, forming the ring and which may be fused to one aromatic ring as described for aryl, which include cyclopropyl,

cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,

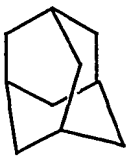
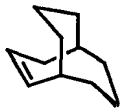
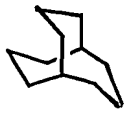
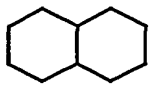
 ,  ,  ,  ,

any of which groups may be optionally substituted with 1 to 4 substituents which may be any of the R^1 groups, or the R^1 substituents set out herein.

The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 5 to 20 carbons, preferably 6 to 12 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

The term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkylalkyl, cycloalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, aminoalkyl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio,

cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,

 ,  ,  ,  ,

any of which groups may be optionally substituted with 1 to 4 substituents which may be any of the R^1 groups, or the R^1 substituents set out herein.

The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 5 to 20 carbons, preferably 6 to 12 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

The term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkylalkyl, cycloalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, aminoalkyl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio,

arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkyl-aminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfon-aminocarbonyl or any of the R^1 groups or the R^1 substituents set out herein.

The term "aralkyl", "aryl-alkyl" or "aryllower alkyl" as used herein alone or as part of another group refers to alkyl groups as discussed above having an aryl substituent, such as benzyl or phenethyl, or naphthylpropyl, or an aryl as defined above.

The term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

The term "amino" as employed herein alone or as part of another group may optionally be independently substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. These substituents may be further substituted with a carboxylic acid or any of the R^1 groups or R^1 substituents thereof as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

The term "lower alkylthio", alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of

another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

The term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

The term "acyl" as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl $\left(\begin{smallmatrix} O \\ \| \\ C \end{smallmatrix}\right)$ group; examples of acyl groups include any of the R^1 groups attached to a carbonyl, such as alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, cycloheteroalkanoyl and the like.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 3 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonyl-amino, nitro, cyano, thiol, alkylthio or any of the R^1 groups, or the R^1 substituents set out herein.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain

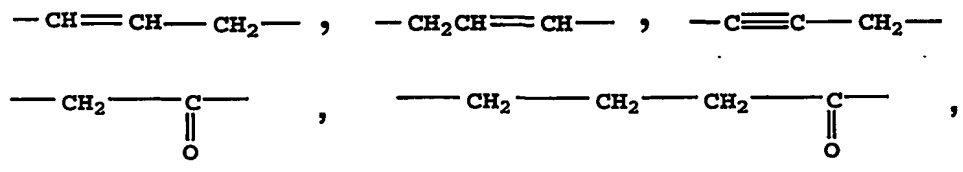
radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, or any of the R^1 groups, or the R^1 substituents set out herein.

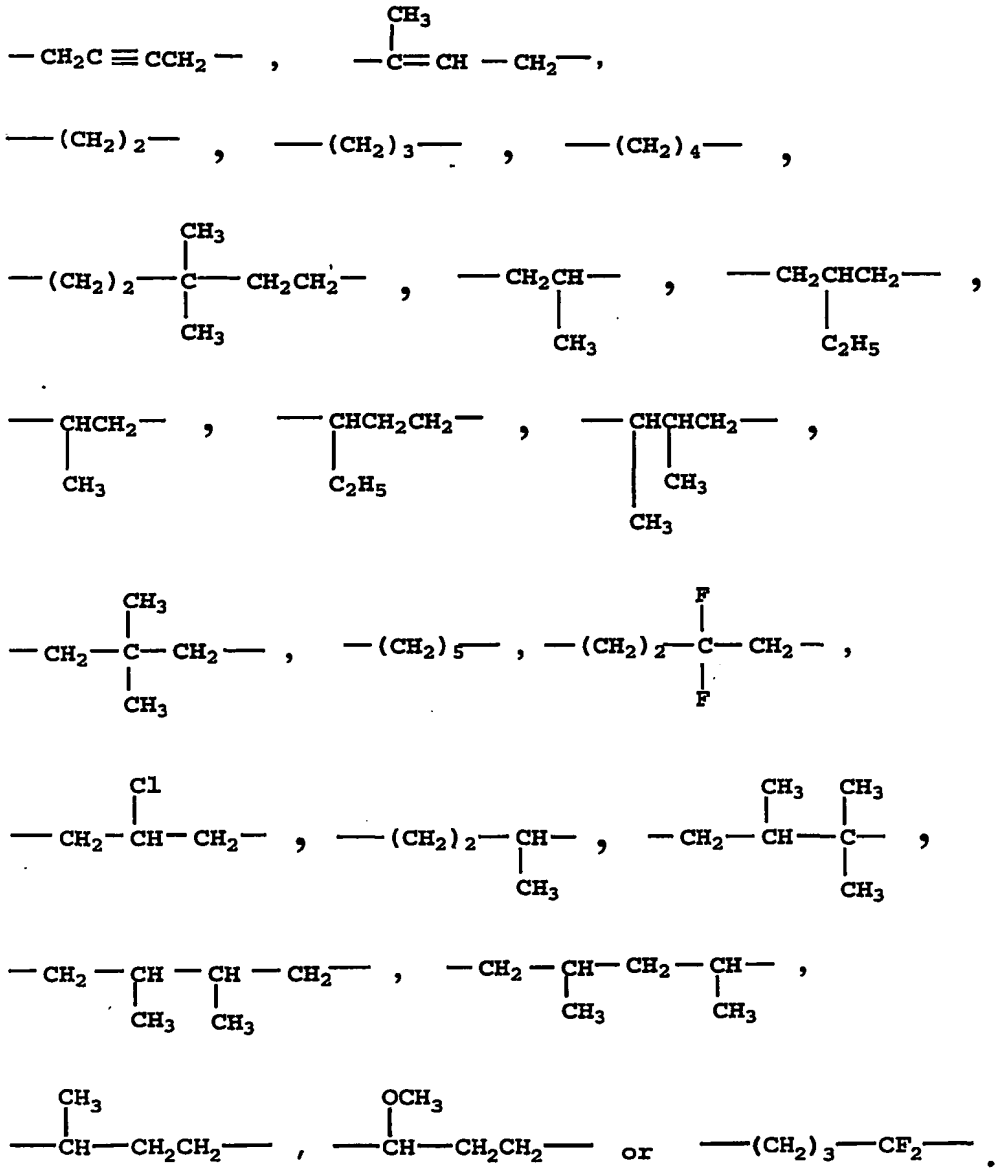
Where alkyl groups as defined above have single bonds for attachment to other groups at two different carbon atoms, they are termed "alkylene" groups and may optionally be substituted as defined above for "alkyl".

Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are termed "alkenylene groups" and "alkynylene groups", respectively, and may optionally be substituted as defined above for "alkenyl" and "alkynyl".

Suitable alkylene, alkenylene or alkynylene groups $(CH_2)_p$ (where, p is 1 to 8, preferably 1 to 5) (which may include alkylene, alkenylene or alkynylene groups) as defined herein, may optionally include 1, 2, or 3 substituents which include any of the R^1 groups, or the R^1 substituents set out herein.

Examples of alkylene, alkenylene and alkynylene include



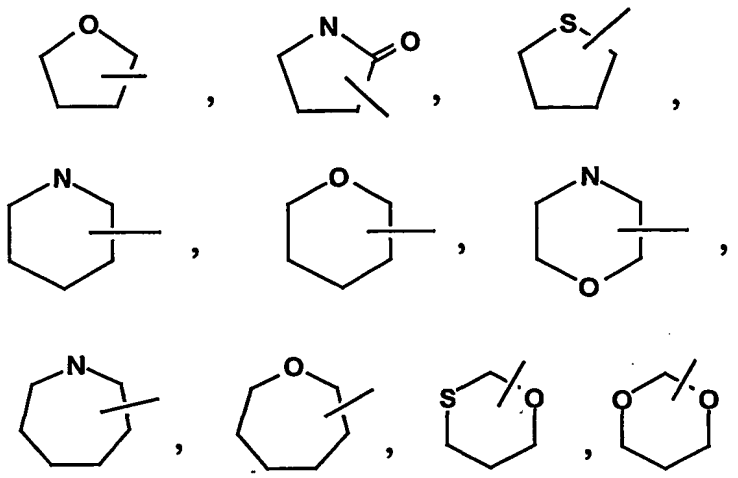


The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or fluorine being preferred.

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

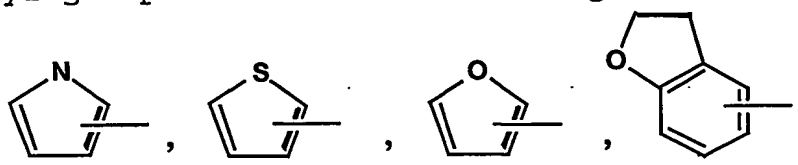
The term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-

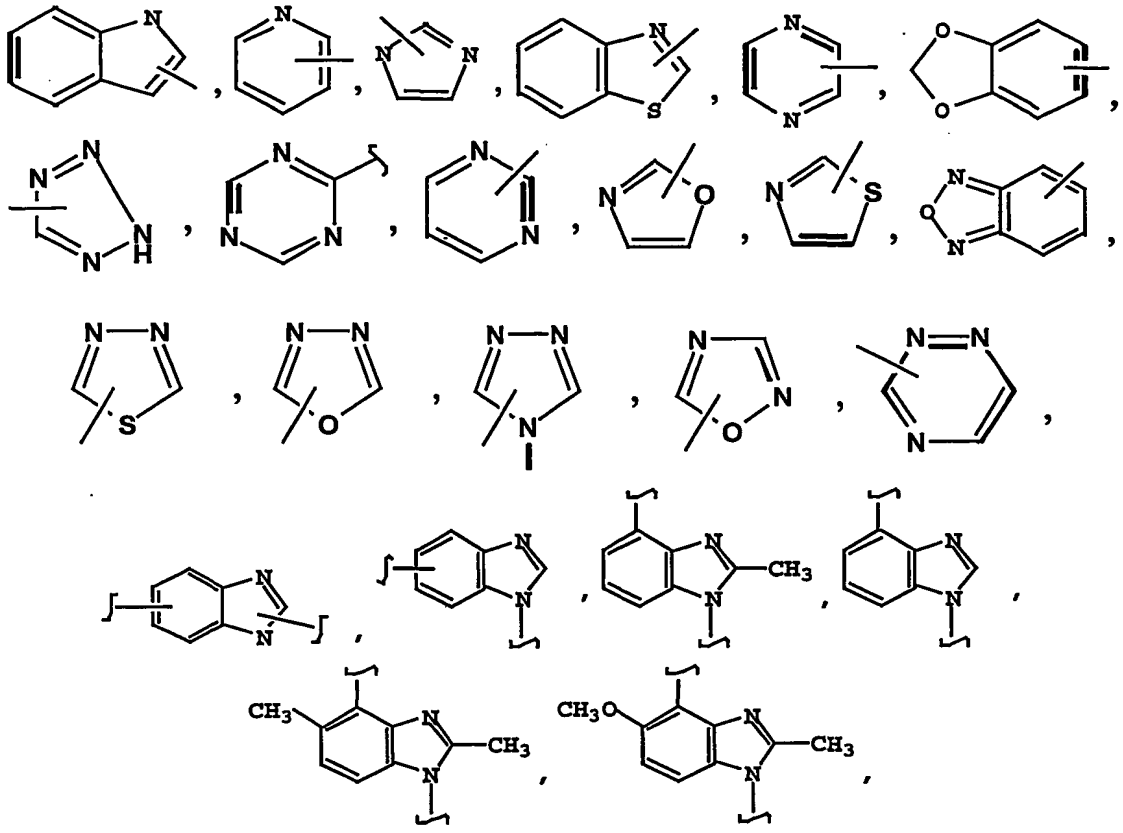
membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as



and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of the R^1 groups, or the R^1 substituents set out herein. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

The term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as any of the R^1 groups or the R^1 substituents set out above. Examples of heteroaryl groups include the following:





and the like.

The term "cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(CH_2)_p$ chain.

The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(CH_2)_p-$ chain, alkylene or alkenylene as defined above.

The term "polyhaloalkyl" as used herein refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2, CF_3 or $CF_3CF_2CH_2$.

The term "polyhaloalkyloxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2O, CF_3O or $CF_3CF_2CH_2O$.

The compounds of formula I can be present as salts, in particular pharmaceutically acceptable salts. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C_1-C_4)-alkyl- or aryl-sulfonic acids which are unsubstituted or substituted, for example by halogen, for example methane- or p-toluene-sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of formula I having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethyl-propylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or

purification of free compounds I or their pharmaceutically acceptable salts, are also included.

Preferred salts of the compounds of formula I include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When enantiomeric or diastereomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

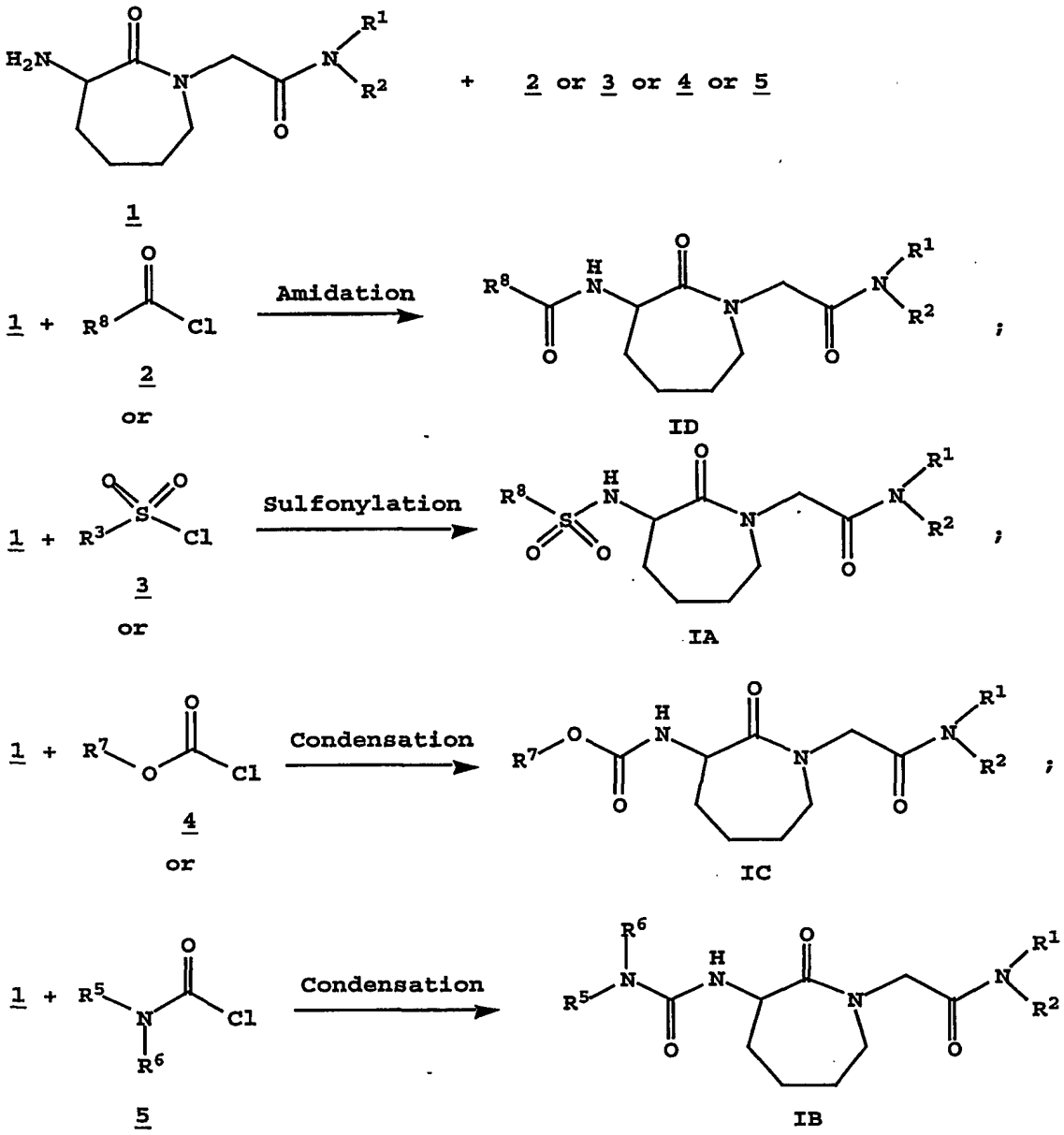
It should be understood that the present invention includes prodrug forms of the compounds of formula I such as alkylesters of acids or any known prodrugs for lactam derivatives.

The compounds of the instant invention may, for example, be in the free or hydrate form, and may be obtained by methods exemplified by the following descriptions.

The compounds of formula I may be prepared by the exemplary processes described in the following reaction schemes. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples.

Compounds of formula I of the invention can be prepared from the corresponding amine 1 by using the sequence of steps outlined in Scheme I set out below.

Reaction Scheme I

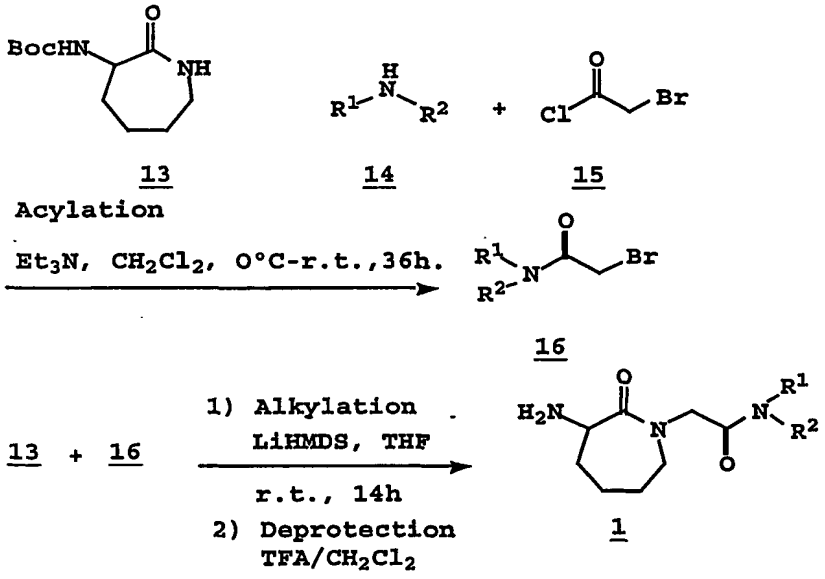


Reaction of amine 1 in an inert organic solvent such as dichloromethane, chloroform or tetrahydrofuran with reactant acid chloride 2, sulfonyl chloride 3, chloroformate 4 or carbamoylchloride 5, employing a molar ratio of reactant:amine 1 within the range from about 5:1 to about 1:5, optionally in the presence of an acid scavenger such as triethylamine, diisopropylethylamine,

pyridine, or polyvinylpyridine, forms compounds ID, IA, IC or IB of the invention.

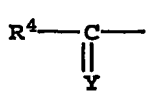
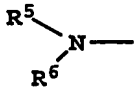
Starting compound 1 can be prepared by methods known in the art as outlined in Reaction Scheme IA below.

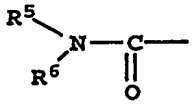
Reaction Scheme IA



Compound 1 is a novel compound provided that R^1 and R^2 are as defined herein, but excludes alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or polycycloalkyl.

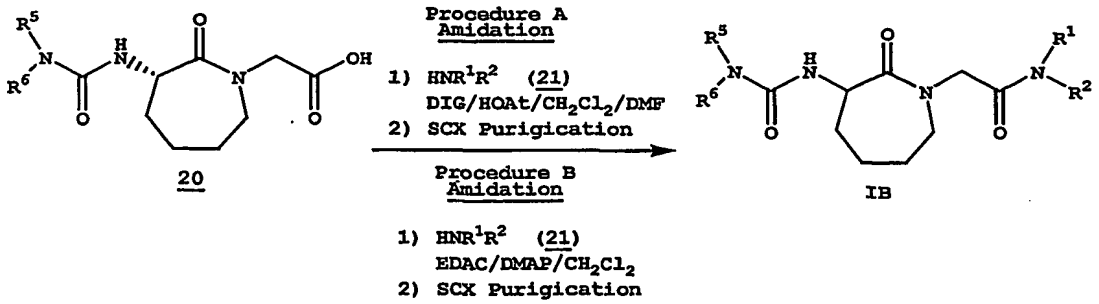
Compounds of formula I of the invention wherein

X is  , Y is O and R^4 is  ,

that is 

can be prepared from the corresponding acid 6 by using the sequence of steps outlined in Scheme II (Procedures A and B) set out below.

Reaction Scheme II



Procedure A: For amines where R^1 or R^2 contain additional basic nitrogens.
Procedure B: For amines where R^1 or R^2 contain no additional basic nitrogens.

In Procedure A (for amines where R^1 or R^2 contain additional basic nitrogens), a mixture of a solution of amine 21 in an inert organic solvent such as THF, methylenechloride or chloroform, a carbodiimide such as diisopropylcarbodiimide (DIC) and 7-aza-1-hydroxy-benzotriazole (HOAt) is reacted with acid 20, employing a molar ratio of amine 21:acid 20 within the range from about 5:1 to about 1:5, preferably at about 1:1.1, to form a reaction mixture which is purified via an SCX column to separate out compound IB of the invention.

The DIC will be employed in a molar ratio to acid 20 within the range from about 5:1 to about 1:5, preferably at about 1.6:1, and the HOAt will be employed in a molar ratio acid 20 within the range from about 5:1 to about 1:5, preferably at about 1.6:1.

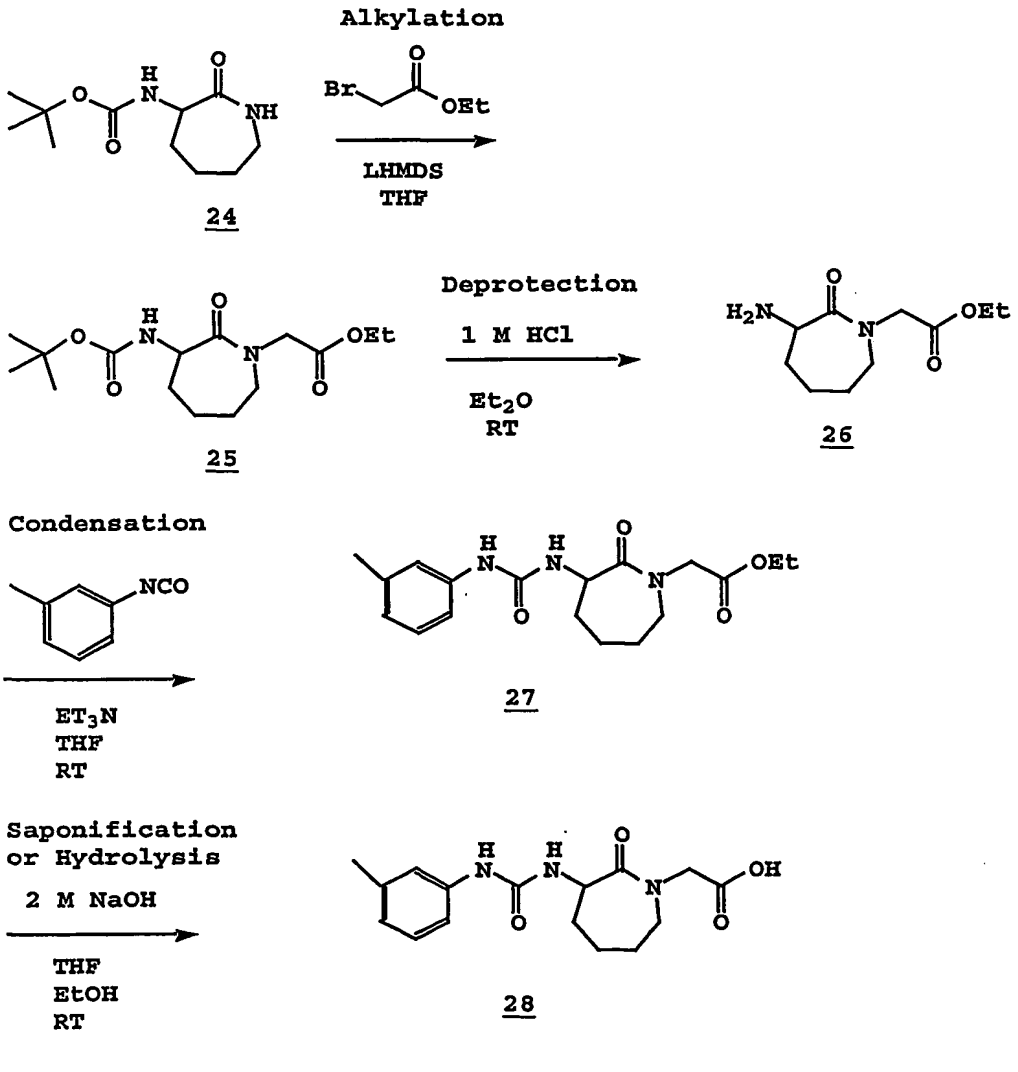
In Procedure B (for amines where R^1 and/or R^2 contain no additional basic nitrogens) a mixture of a solution of amine 21 in an inert organic solvent such as THF , methylenechloride or chloroform, ethyldimethylaminopropylcarbodiimide (EDAC) and dimethylaminopyridine (DMAP) with acid 20, employing a molar ratio of amine 21:acid 20 within the range from about 5:1 to about 1:5, preferably at about 1.5:1, to

form a reaction mixture which is purified via a SCX column to separate out compound IB of the invention.

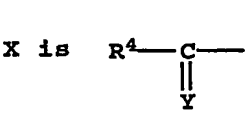
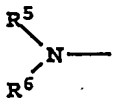
The EDAC will be employed in a molar ratio to acid 20 within the range from about 5:1 to about 1.5, preferably at about 1.5:1, and the DMAP will be employed in a molar ratio to acid 20 within the range from about 5:1 to about 1:5, preferably at about 1.5:1.

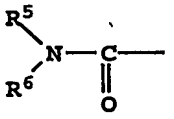
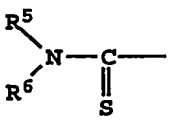
Starting compound 20 can be prepared by methods known in the art as outlined in Reaction Scheme IIA.

Reaction Scheme IIA



Compounds of formula I of the invention wherein

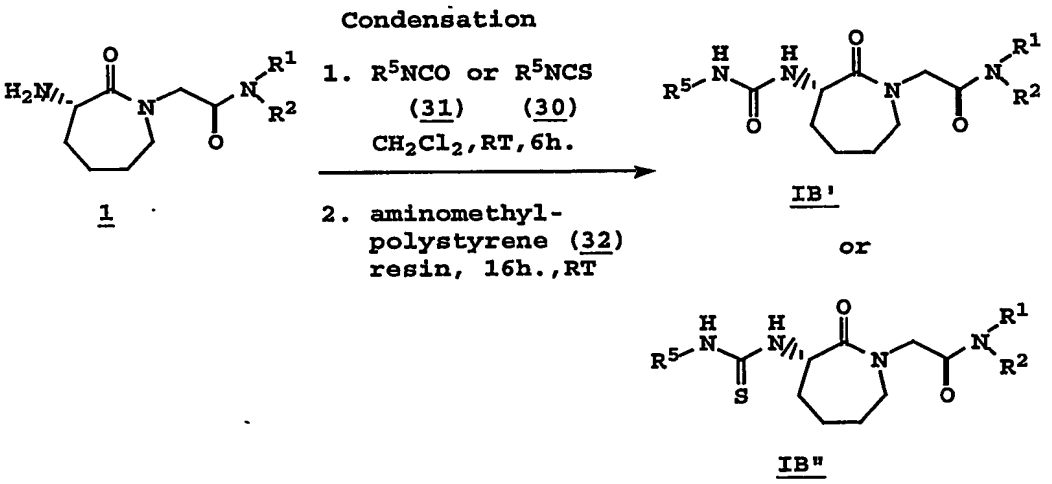
X is  , Y is O or S, and R^4 is  ,

that is  or 

can be prepared from the corresponding amine 1 by using the sequence of steps outlined in Scheme III set out below.

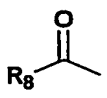
Reaction Scheme III

25

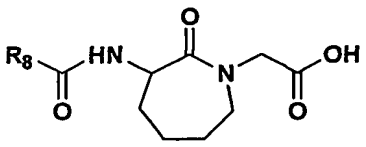


Reaction of amine 1 (in an inert organic solvent such as dichloromethane, chloroform or tetrahydrofuran) with reactant 30 or 31 employing a molar ratio of 30 or 31:amine 1 within the range of from about 5:1 to about 1:5, followed by treatment with aminomethylpolystyrene (32), affords the compound of the invention IB' or IB".

Compounds of formula I of the invention wherein

X = 

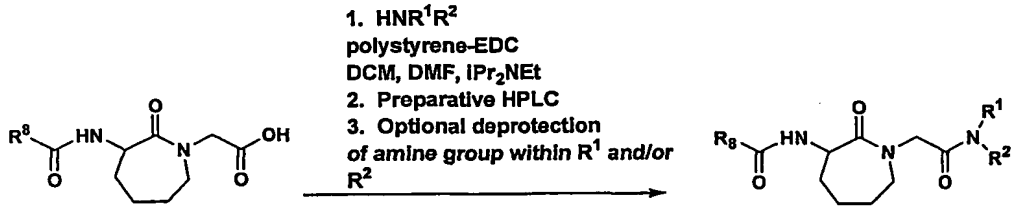
can be prepared from the corresponding acid 29



29

using the sequence of steps outlined in Scheme IV set out below:

Reaction Scheme IV

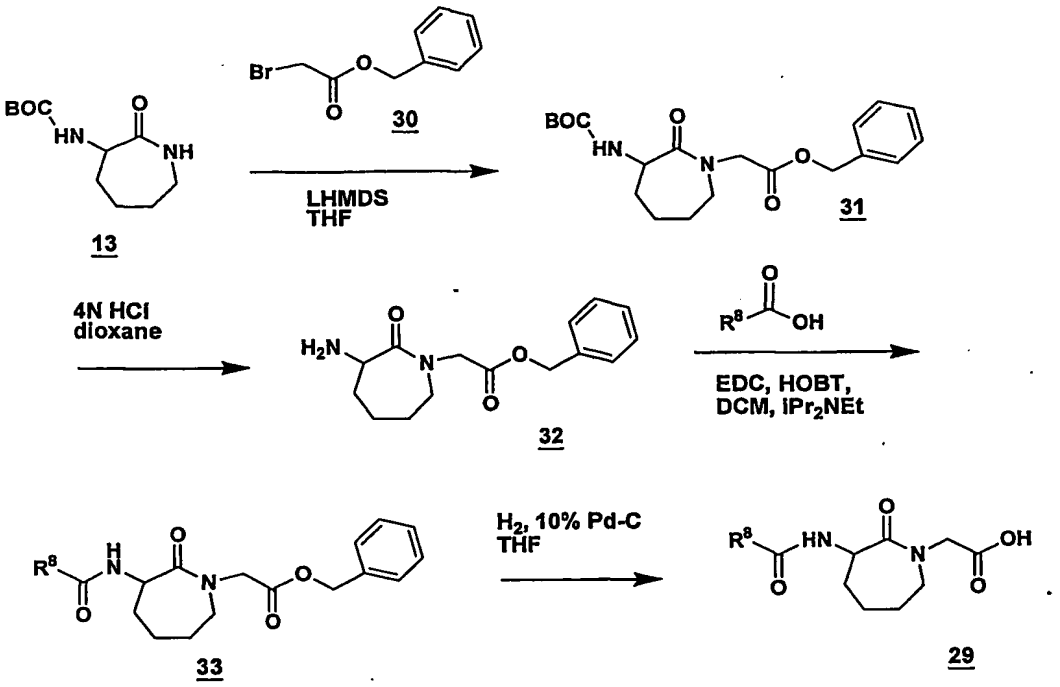


29 ID1

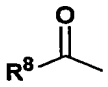
R^1 and/or R^2 can be neutral or may contain a basic nitrogen. When R^1 or R^2 contains a basic nitrogen, the nitrogen may optionally be protected, for example with a BOC group or Cbz group. The protecting group can then be removed, for example, by treating with TFA in methylene chloride for removal of a BOC or Cbz protecting group.

Starting compound 29 can be prepared by methods as outlined in Reaction Scheme IVa

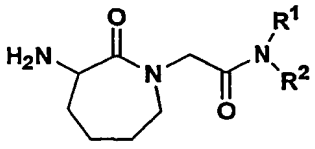
Reaction Scheme IVa



Alternatively, compounds of formula I of the invention wherein

X = 

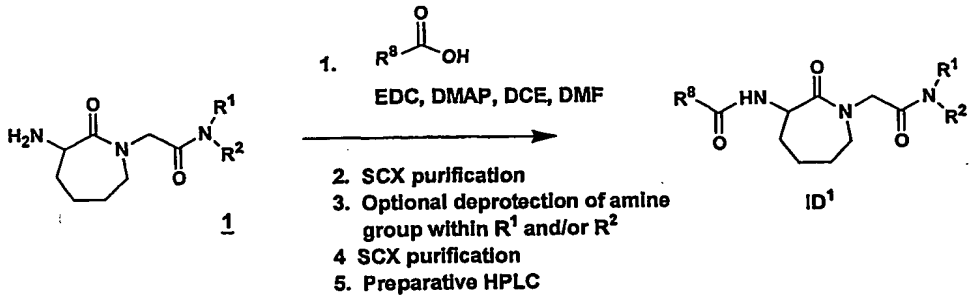
can be prepared from the corresponding amine 1



1

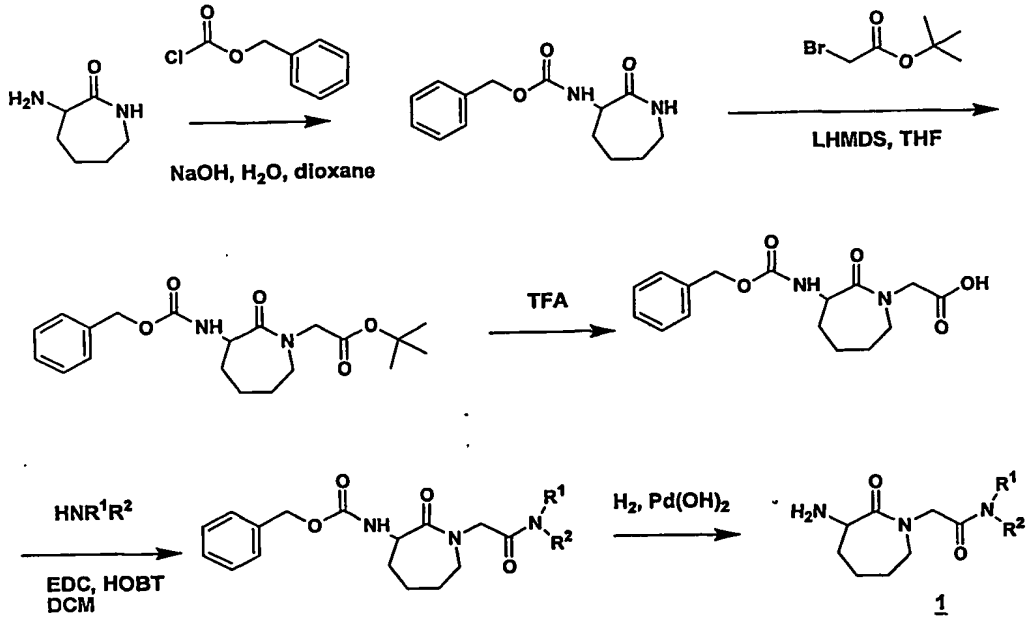
using the sequence of steps outline in Scheme V set out below.

Reaction Scheme V:



R^1 and/or R^2 can be neutral or may contain a basic nitrogen. When R^1 or R^2 in starting amine 1 contains a basic nitrogen, the nitrogen may optionally be protected, for example, with a BOC group. The protecting group can then be removed, for example, by treating with TFA in methylene chloride for removal of a BOC protecting group, as outlined below in Reaction Scheme VA.

Reaction Scheme VA



The novel compounds of formula I of the invention possess tryptase inhibition activity. This activity was confirmed using either isolated human skin tryptase or recombinant human tryptase prepared from the human

recombinant beta-protryptase expressed by baculovirus in insect cells. The expressed beta-protryptase was purified using sequential immobilized heparin affinity resin followed by an immunoaffinity column using an anti-tryptase monoclonal antibody. The protryptase was activated by auto-catalytic removal of the N-terminal in the presence of dextran sulfate followed by dipeptidyl peptidase I (DPPI) removal of the two N-terminal amino acids to give the mature active enzyme (Sakai et al, J. Clin. Invest., 97, pages 988-995, 1996). Essentially equivalent results were obtained using isolated native enzyme or the activated expressed enzyme. The tryptase enzyme was maintained in 2M sodium chloride, 10 nM 4-morpholine-propanesulfonic acid, pH 6.8.

The assay procedure employed a 96 well microplate. To each well of the microplate (Nunc MaxiSorp), 250 µl of assay buffer [containing low molecular weight heparin and tris (hydroxymethyl)aminomethane] was added followed by 2.0 µl of the test compound in dimethylsulfoxide. The substrate (10 µl) was then added to each well to give a final concentration of either 370 µM benzoyl-arginine-*p*-nitroaniline (BAPNA) or 100 µM benzyloxycarbonyl-glycine-proline-arginine-*p*-nitroaniline (CBz-Gly-Pro-Arg-pNA). Similar data was obtained using either substrate. The microplate was then shaken on a platform vortex mixer at a setting of 800 (Sarstedt TPM-2). After a total of three minutes incubation, 10 µl of the working stock solution of tryptase (6.1 mM final tryptase concentration for use with BAPNA or 0.74 nM for use with CBz-Gly-Pro-Arg-pNA) was added to each well. The microplate was vortexed again for one minute and then incubated without shaking at room temperature for an additional 2 minutes. After this time the microplate was read on a microplate reader (Molecular Devices UV max) in the kinetic mode (405 nm wavelength) over twenty minutes at room temperature. To determine the compound concentration that inhibited half of the enzyme activity (IC_{50}), the

fraction of control activity (FCA) was plotted as a function of the inhibitor concentration and curve to fit FCA/(1[I]/IC_{50}). The IC_{50} for each compound was determined 2-4 times and the obtained values were averaged.

As a result of this tryptase activity, the compounds of formula I as well as a pharmaceutically acceptable salt thereof, are useful as anti-inflammatory agents particularly in the treatment and/or prevention of chronic asthma and may also be useful in treating and/or preventing allergic rhinitis, inflammatory bowel disease, psoriasis, conjunctivitis, atopic dermatitis, rheumatoid arthritis, osteoarthritis, and other chronic inflammatory joint diseases, or diseases of joint cartilage destruction. Additionally, these compounds may be useful in treating or preventing myocardial infarction, stroke, angina and other consequences of atherosclerotic plaque rupture. Additionally, these compounds may be useful for treating or preventing diabetic retinopathy, tumor growth and other consequences of angiogenosis. Additionally, these compounds may be useful for treating or preventing fibrotic conditions, for example, fibrosis, scleroderma, pulmonary fibrosis, liver cirrhosis, myocardial fibrosis, neurofibromas and hypertrophic scars. Additionally these compounds may be useful for treating and/or preventing diseases involving angiogenesis including, but not limited to, cancer.

The compounds of the present invention may be used in combination with β-adrenergic agonists such as albuterol, terbutaline, formoterol, salmeterol, bitolterol, pilbuterol, or fenoterol, as well as with anticholinergics such as ipratropium bromide, anti-inflammatory cortiocosteroids such as beclomethasone, triamcinolone, budesonide, fluticasone, flunisolide or dexamethasone, and anti-inflammatory agents such as cromolyn, nedocromil, theophylline, zileuton, zafirlukast, monteleukast and pranleukast, and/or hypolipodemic agents such as pravastatin, simvastatin,

atorvastatin, fluvastatin, cerivastatin, itavastatin (pitavastatin, NK-104), or visastatin (or rosuvastatin).

The compounds of the invention can be administered orally or parenterally such as subcutaneously or intravenously, as well as by inhalation and nasal application, rectally, transdermally, or sublingually to various mammalian species known to be subject to such maladies, e.g., humans, cats, dogs and the like in an effective amount within the dosage range of about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 mg) on a regimen in single or 2 to 4 divided daily doses.

The active substance can be utilized in a composition such as tablet, capsule, solution or suspension or in other type carrier materials such as transdermal devices, iontophoretic devices, rectal suppositories, inhalant devices and the like. The composition or carrier will contain about 5 to about 500 mg per unit of dosage of a compound or mixture of compounds of formulas I, IA., IB, IC and ID. They may be compounded in conventional matter with a physiologically acceptable vehicle or carrier, excipient, binder, preservative, stabilizer, flavor, etc., as called for by accepted pharmaceutical practice.

The following abbreviations are employed hereinbefore and in the Examples:

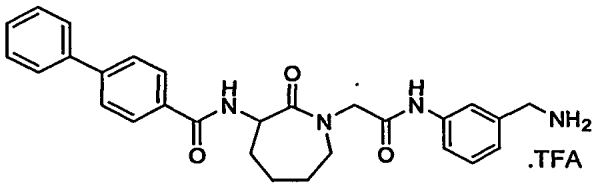
Ph = phenyl
Bn = benzyl
t-Bu = tertiary butyl
Me = methyl
Et = ethyl
TMS = trimethylsilyl
$TMSN_3$ = trimethylsilyl azide
TBS = tert-butyldimethylsilyl
FMOC = fluorenylmethoxycarbonyl
Boc = tert-butoxycarbonyl
Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl
THF = tetrahydrofuran

Et_2O = diethyl ether
hex = hexanes
EtOAc = ethyl acetate
DMF = dimethyl formamide
MeOH = methanol
EtOH = ethanol
i-PrOH = isopropanol
DMSO = dimethyl sulfoxide
DME = 1,2 dimethoxyethane
EDC or DCE = 1,2 dichloroethane
HMPA = hexamethyl phosphoric triamide
HOAc or AcOH = acetic acid
TFA = trifluoroacetic acid
$i\text{-}Pr_2NEt$ = diisopropylethylamine
Et_3N = triethylamine
NMM = N-methyl morpholine
DMAP = 4-dimethylaminopyridine
$NaBH_4$ = sodium borohydride
$NaBH(OAc)_3$ = sodium triacetoxyborohydride
DIBALH = diisobutyl aluminum hydride
DCM = 4-(dicyanomethylene)-2-methyl-6-(4-dimethylamino-styryl)-4H-pyran
$LiAlH_4$ = lithium aluminum hydride
n-BuLi = n-butyllithium
Pd/C = palladium on carbon
PtO_2 = platinum oxide
KOH = potassium hydroxide
NaOH = sodium hydroxide
LiOH = lithium hydroxide
K_2CO_3 = potassium carbonate
$NaHCO_3$ = sodium bicarbonate
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
EDC (or EDC.HCl) or EDCI (or EDCI.HCl) or EDAC = 3-ethyl-3'-(dimethylamino)propyl- carbodiimide hydrochloride (or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride)
HOBT or $HOBT.H_2O$ = 1-hydroxybenzotriazole hydrate
HOAT = 1-Hydroxy-7-azabenzotriazole
BOP reagent = benzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluorophosphate
$NaN(TMS)_2$ = sodium hexamethyldisilazide or sodium bis(trimethylsilyl)amide
Ph_3P = triphenylphosphine
$Pd(OAc)_2$ = Palladium acetate
$(Ph_3P)_4Pd^o$ = tetrakis triphenylphosphine palladium
DEAD = diethyl azodicarboxylate
DIAD = diisopropyl azodicarboxylate
Cbz-Cl = benzyl chloroformate
CAN = ceric ammonium nitrate
SAX = Strong Anion Exchanger
SCX = Strong Cation Exchanger
Ar = argon

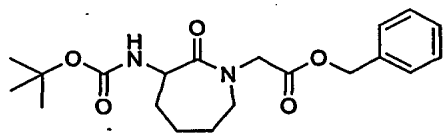
N_2 = nitrogen
min = minute(s)
h or hr = hour(s)
L = liter
mL = milliliter
μL = microliter
g = gram(s)
mg = milligram(s)
mol = moles
mmol = millimole(s)
meq = milliequivalent
RT = room temperature
sat or sat'd = saturated
aq. = aqueous
TLC = thin layer chromatography
HPLC = high performance liquid chromatography
LC/MS = high performance liquid chromatography/mass spectrometry
MS or Mass Spec = mass spectrometry
NMR = nuclear magnetic resonance
mp = melting point

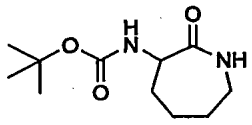
The following working Examples represent preferred embodiments of the present invention.

Example 1



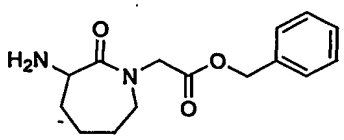
A.





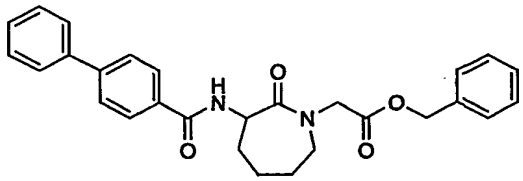
To a solution of (16.77 g, 73.6 mmol, 1.0 eq) in THF (400 mL) under a nitrogen atmosphere at -78°C was added LiHMDS (1.0 M in THF, 150 mL, 150 mmol, 2.04 eq) dropwise via an addition funnel over 10 minutes. The resulting mixture was stirred for an additional 10 minutes at -78°C, warmed to room temperature and stirred at room temperature for 1 hour. The reaction mixture was then cooled to -78°C and phenyl 2-bromoacetate (14 mL, 88.3 mmol, 1.2 eq) was added. The reaction mixture was warmed to room temperature and stirred for 18 hours. 1N $KHSO_4$ was added until the pH remained neutral. NaCl (~5 g) was added to the resulting bi-phasic solution. After the layers were mixed and allowed to separate, the upper THF layer was removed and set aside and the aqueous layer was extracted once with EtOAc. The combined THF and EtOAc extracts were dried over $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography provided 21g of title compound (75.7%). MS: m/z 399 $(M + Na)^+$.

B.



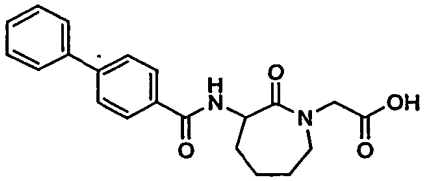
A solution of Part A compound (7.0 g, 18.59 mmol, 1.0 eq) in 4 M HCl in dioxane (25 mL) was stirred at room temperature for 1.5 hours. Solvents were removed and the residue was reconstituted in CH_2Cl_2/Et_2O to give 6.0 g of an off-white precipitate. Re-crystallization from CH_2Cl_2/Et_2O afforded 5.14 g (88%)of title compound as a white solid. MS: m/z 277 $(M+H)^+$.

C.



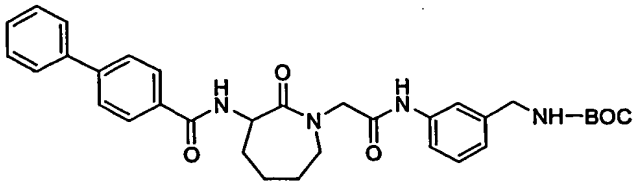
A solution of Part B compound (2.7 g, 8.63 mmol, 1 eq), EDC (1.98 g, 10.3 mmol, 1.2 eq), HOBT (1.40 g, 10.35 mmol, 1.2 eq) in CH_2Cl_2 (100 mL) at 0°C was treated with iPr_2NEt (6.0 mL, 34.5 mmol, 4 eq). The reaction mixture was brought to room temperature and 4-biphenylcarboxylic acid (2.05 g, 10.35 mmol, 1.2 eq) was added. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was then diluted with CH_2Cl_2, washed with 5% $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography gave 2.16g (55%) of title compound as a white foam. MS: m/z 479 $(M+Na)^+$.

D.

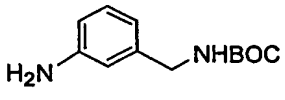


To a solution of Part C compound (4.5 g, 9.86 mmol, 1.0 eq) in THF (200 mL) at RT was added 10%Pd/C (3 g) followed by bubbling of H_2 through the solution for 1 hour. The reaction was then stirred under H_2 for 4 hours. The reaction mixture was filtered through a pad of celite and the pad was rinsed twice with THF (2x25 mL). Solvent was removed to provide 3.62 g (100%) of title compound as a white solid. MS: m/z 367 $(M+H)^+$.

E.

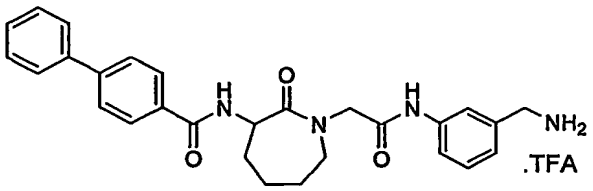


Part E compound was prepared as part of a semi-automated parallel library.

To a 16x100 mm reaction tube was added Part D compound (30 mg, 0.082 mmol, 1.0 eq), polystyrene-EDC (Advanced Chemtech catalog #SP5005,100 mg, 0.8 mmol/g, 0.08 mmol, 0.98 eq), iPr_2NEt (0.05 mL, 0.29 mmol, 3.5 eq) and amine 

(14 mg, 0.063 mmol, 0.77 eq) in DMF (0.6 mL) and DCE (1.0 mL), and was shaken for 3 days. Additional polystyrene-EDC (50 mg, 0.8 mmol/g, 0.04 mmol, 0.49 eq) and DCE (0.5 mL) were added and the reaction mixture was shaken for an additional 24 hours. To the reaction mixture was added Polystyrene-Trisamine (Argounaut Tech, 50 mg, 6.8 mmol/g, 0.34 mmol, 4.15 eq) as a scavenger resin and the reaction mixture was shaken for 24 hours. The reaction mixture was filtered and the eluent was concentrated using a speed vac. Purification by reverse phase preparative HPLC (Shimadzu VP-ODS, flow rate 20 mL/min) followed by concentration using a speed vac gave analytically pure title compound. MS: m/z 593 $(M+Na)^+$.

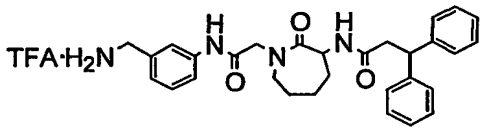
F.



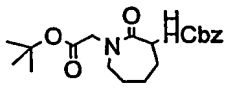
For compounds from the above semi-automated parallel library having BOC protecting groups, deprotection was carried out using the following procedure.

Part E compound was taken up in 10% TFA in DCE (5 mL) and let set for 2 hours. Concentration using a speed vac then afforded 4.8 mg (10% from Part D compound) of title compound. MS: m/z 471 $(M+H)^+$.

Example 2



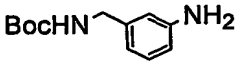
A.



(Caprolactam)

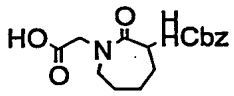
The title compound is a known compound as disclosed in Skiles, J.W., et al, Bioorg. Med. Chem. Lett., 1993, 3, 773.

B. 3-Boc-aminomethyl aniline



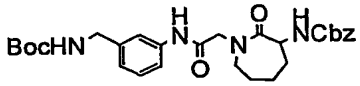
The title compound is a known compound as disclosed in Collins, J.L., et al, J. Med. Chem., 1998, 41, 2858.

C.



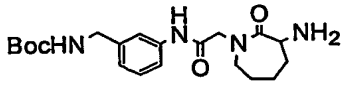
TFA (20 mL) was slowly added to a solution of Part A compound (8.64 g, 22.95 mmol) in CH_2Cl_2 (30 mL) at 0°C. The reaction mixture was then stirred at room temp. After 24 h the solution was concentrated. The residue was dissolved in $CHCl_3$ (50 mL) and the solution was concentrated. This was repeated 2 more times. A portion of the crude product was purified by silica gel chromatography giving 2.90 g of title compound.

D.



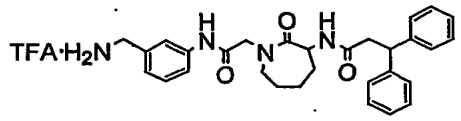
EDAC-HCl (1.74 g, 9.05 mmol) was added to a stirred solution of Part B compound (2.01g, 9.05 mmol), Part C compound (2.90 g, 9.05 mmol) and HOBt (1.22 g, 9.05 mmol) in CH_2Cl_2 (35 mL) at 0°C. NMM (1.04 mL, 9.50 mmol) was added and the reaction mixture was stirred at room temp. After 24 h the solution was diluted with CH_2Cl_2 (100 mL) and washed with 5% $KHSO_4$ (50 mL), sat. $NaHCO_3$ (50 mL), and sat NaCl (50 mL). The solution was dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel chromatography to afford 3.60 g (78%) of title compound.

E.

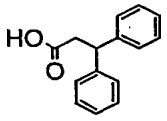


20% $Pd(OH)_2$ (0.34 g) was added to a stirred solution of Part D compound (3.39g, 6.65 mmol) in MeOH (25 mL). A H_2 atmosphere was introduced via balloon. After 24 h the solution was filtered and the filtrate was concentrated to give 2.44 g (94%) of title compound.

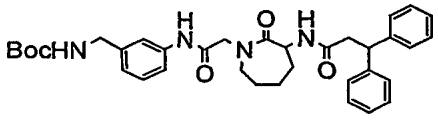
F.



To a reaction tube was added via liquid handler 320 µL (10.8 mg, 0.048 mmol) of a 0.15 M stock solution of



in DMF. 0.30 mL of a DCE solution containing EDC (10.5 mg, 0.055 mmol) and DMAP (6.7 mg, 0.055 mmol) was added manually via syringe. 0.30 mL of a DCE solution containing Part E compound (18.8 mg, 0.050 mmol) was added via the liquid handler. The reaction tube was mixed on an orbital shaker for 12 h. The reaction mixture was then drained through a SCX cation exchange column (0.30 g of absorbent) which was preconditioned with MeOH (0.30 mL) into a 2.5 mL microtube. The column was rinsed with CH_2Cl_2 (0.30mL) and MeOH (0.40 mL). The organic solution containing intermediate F(1)

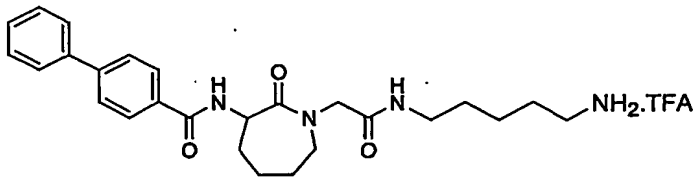


was concentrated by speed vac.

DCE (0.60 mL) was added to the 2.5 mL microtube containing the above intermediate F(1). Upon dissolution TFA (0.30 mL) was added via syringe. The microtube was sealed and shaken using a mini-vortexer. After 3 h the solution was concentrated by speed vac. The product was dissolved in MeOH (1.0 mL) and purified via solid phase extraction using a SCX cation exchange column (0.30 g of absorbent) which was preconditioned with MeOH (0.30 mL). The column was washed with MeOH (2 x 1.5 mL) to remove impurities. The product was then eluted off the column using 2.0 M NH_3 in MeOH (1.5 mL). The eluant was then concentrated by speed vac. The crude product was further purified by PREP HPLC (Shimadzu VP-ODS 20 x 50 mm column) using a gradient of 0 to 100% Solvent B over 5 min and a

flow rate of 20 mL/min. 6.73 mg (23%) of title compound was obtained. Mass spec $(M+H)^+$ = calc'd = 499, found = 499.

Example 3

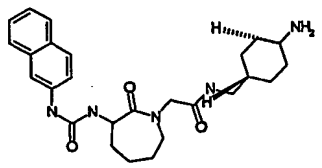
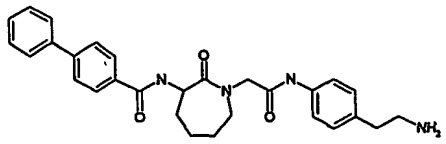
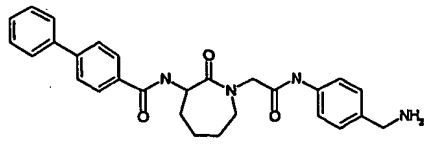
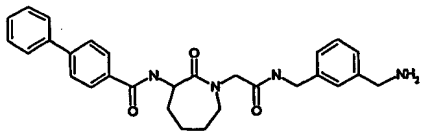
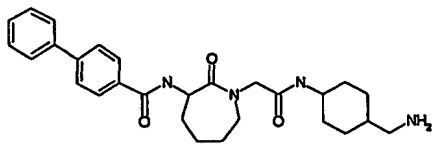
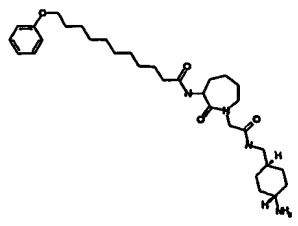
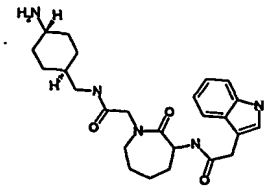


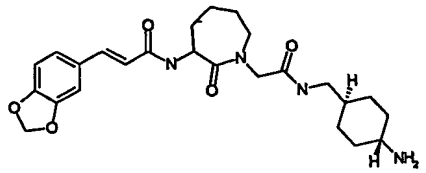
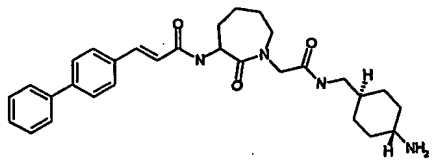
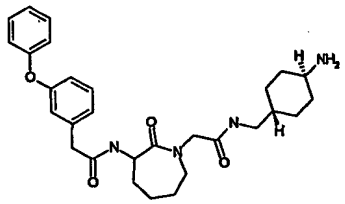
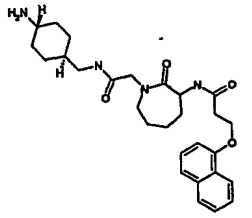
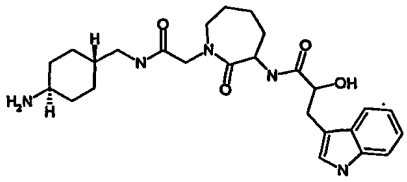
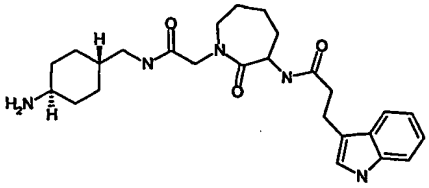
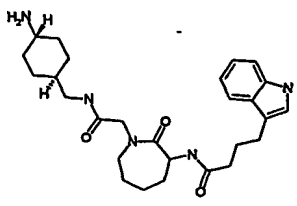
Solution A: To a solution of Example 1 Part D compound (240 mg, 0.655 mmol) in dichloroethane (15 ml) was added DMAP (199 mg, 1.63 mmol) followed by EDC (251 mg, 1.31 mmol). Dichloroethane was added to bring the total volume to 18 ml. This reaction mixture was stirred at room temperature for 2 hours.

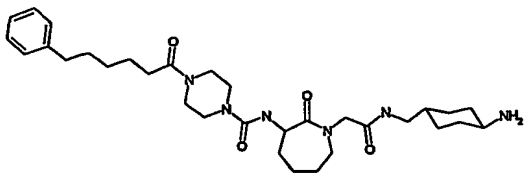
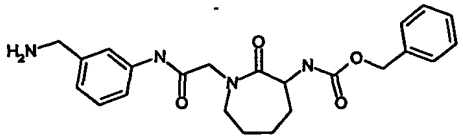
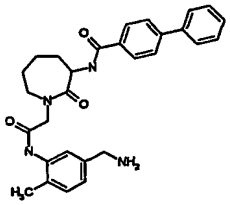
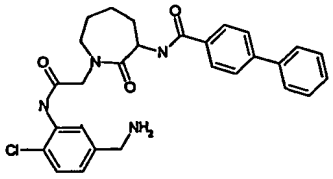
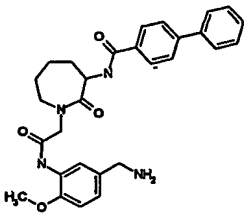
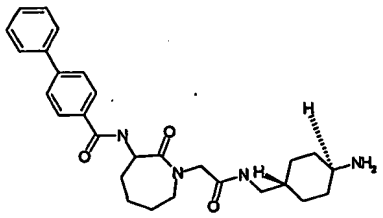
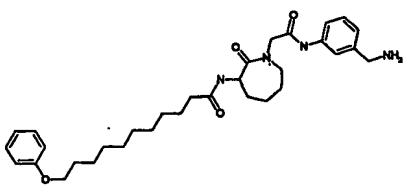
To a 16x100 mm reaction tube containing N-BOC-1,5-diaminopentane (33 mg, 0.164 mmol) was added Solution A (2 ml, 0.073 mmol of Example 60 Part D compound). The reaction tube was capped and warmed to 40°C for 20 hours. The reaction was cooled to room temperature and was then passed through an SCX cartridge (CUBCX12M6). The SCX cartridge was washed with methanol (8 ml) and the eluent was collected. Solvents were removed using a speed vac and the resulting residue was taken up in 30% TFA/dichloroethane (2 ml). After agitating the TFA/dichloroethane solution for 2 hours at room temperature, solvents were removed using a speed vac to afford 19 mg (46%) of title compound. MS: m/z 451.21 $(M+H)^+$.

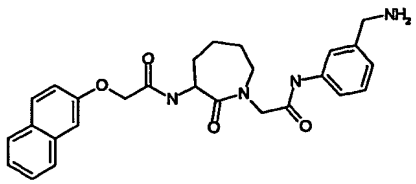
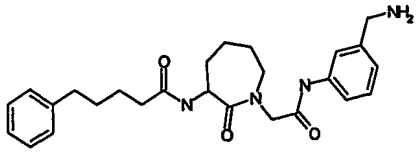
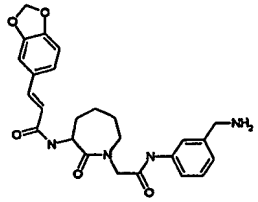
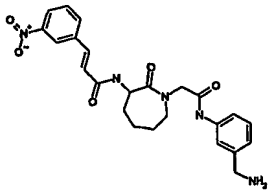
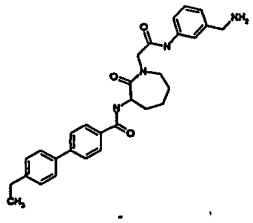
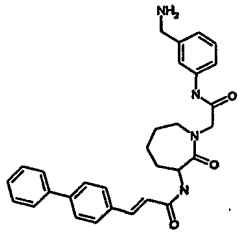
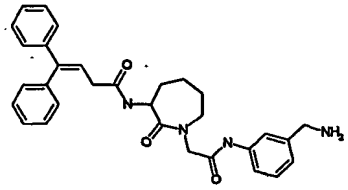
Examples 4 to 103

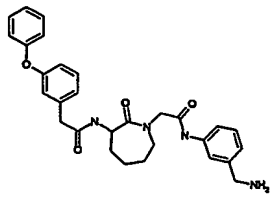
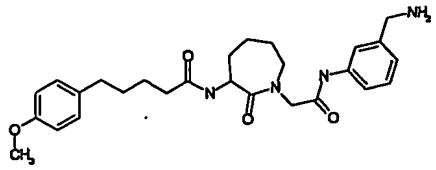
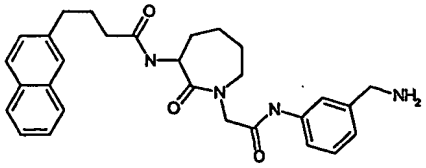
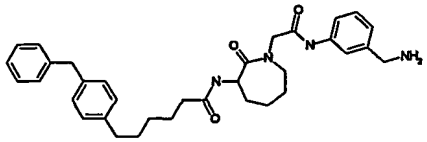
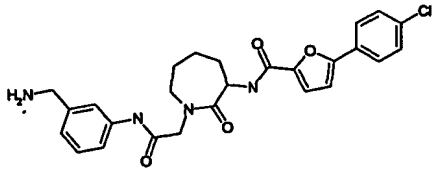
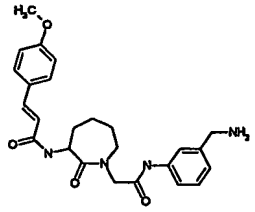
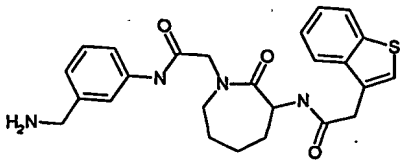
The following compounds were prepared employing procedures as described in previous Examples.

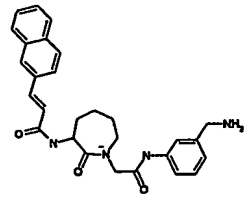
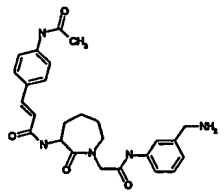
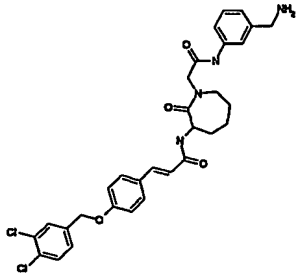
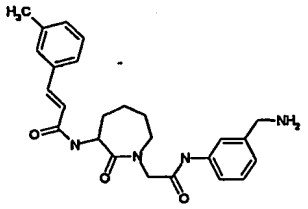
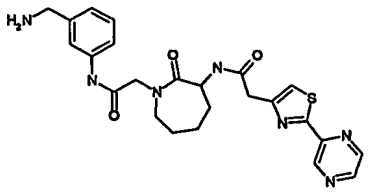
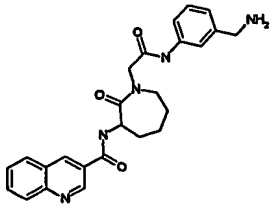
Example No	Structure	Mass Spec. m/z (M+H)*
4		466
5		485
6		471
7		485
8		477
9		557
10		454

11		471
12		503
13		507
14		495
15		484
16		468
17		482

18		583
19		425
20		485
21		506
22		501
23		477
24		551

25		475
26		451
27		465
28		466
29		499
30		497
31		511

32		501
33		481
34		487
35		555
36		495
37		451
38		465

39		471
40		478
41		596
42		435
43		494
44		446

Our Ref: 677105NZ

NEW ZEALAND

PATENTS ACT, 1953

REQUEST FOR POSTPONEMENT OF ACCEPTANCE OF COMPLETE SPECIFICATION [SECTION 20(1A)]

We, QLT Inc., hereby request a postponement of the acceptance of the complete specification of the attached request for entry into the National Phase in New Zealand, to a date not later than the expiration of 15 months from the date on which we fulfil our obligation under Article 22(1) or Article 39(1) of the Patent Cooperation Treaty.

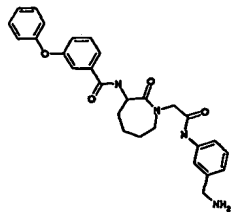
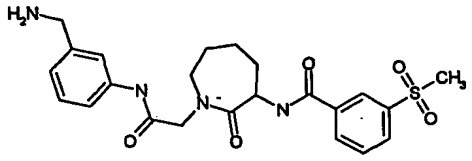
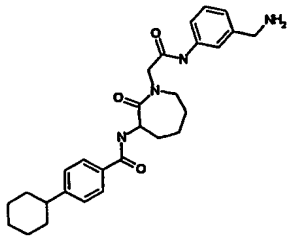
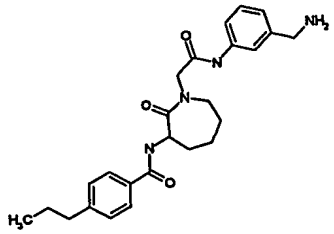
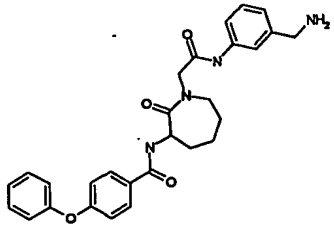
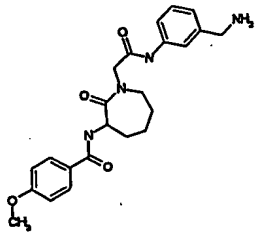
DATED this seventh Day of September, 2005

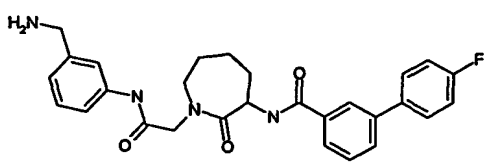
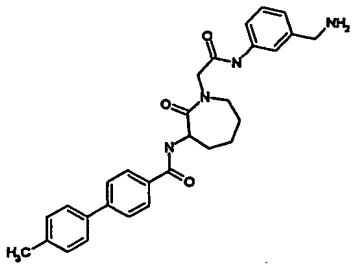
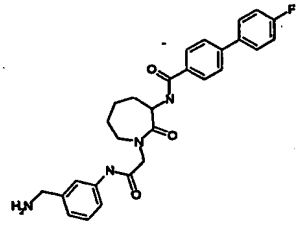
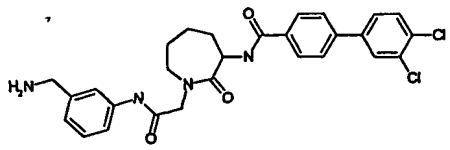
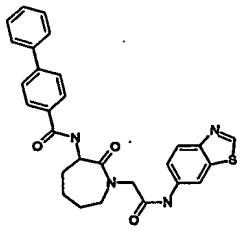
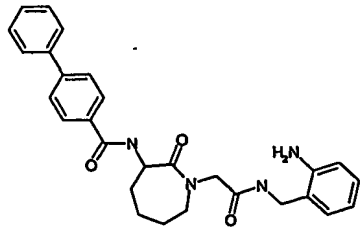
QLT Inc.
By Attorneys for the Applicant
SPRUSON & FERGUSON

Per:

THE COMMISSIONER OF PATENTS
INTELLECTUAL PROPERTY OFFICE OF NEW ZEALAND
LOWER HUTT

Fee: N/A

45		487
46		473
47		477
48		437
49		487
50		425

51		489
52		485
53		489
54		540
55		499
56		471

Our Ref: 677105NZANB

NEW ZEALAND

PATENTS ACT, 1953

NOTICE OF DESIRE FOR EXTENSION OF THE PERIOD FOR PUTTING AN APPLICATION IN ORDER

We, QLT Inc., hereby give notice that we desire the period for putting in order application No. 533036 dated 8 November 2002 to be extended to 3 months from the filing date of the complete specification to 24 December 2005.

Our address for service is as follows:

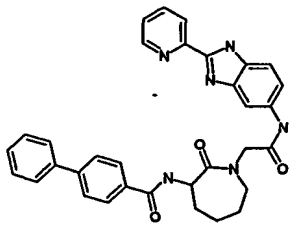
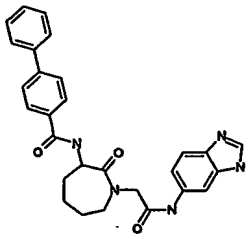
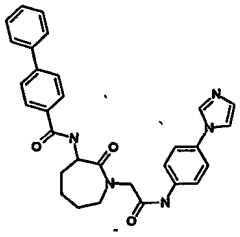
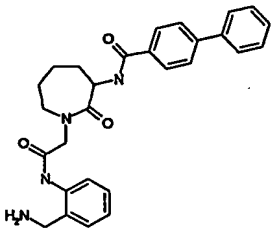
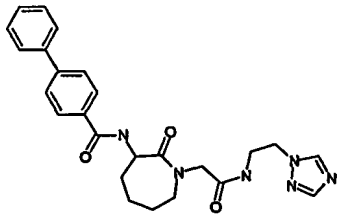
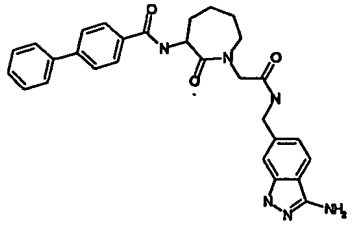
SPRUSON & FERGUSON
PO Box 30461
Lower Hutt
NEW ZEALAND

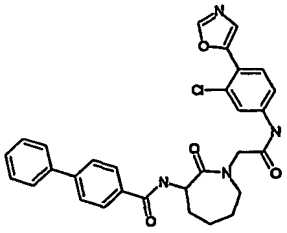
DATED this seventh Day of September, 2005

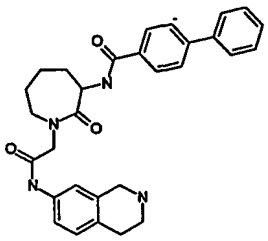
QLT Inc.
By Attorneys for the Applicant
SPRUSON & FERGUSON

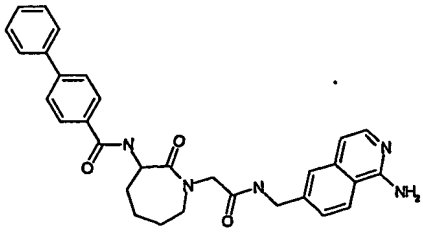
Per:

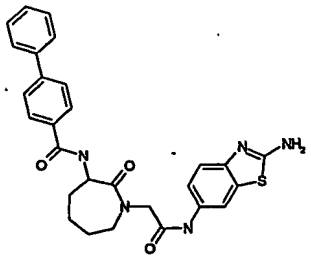
THE COMMISSIONER OF PATENTS
INTELLECTUAL PROPERTY OFFICE OF NEW ZEALAND
LOWER HUTT

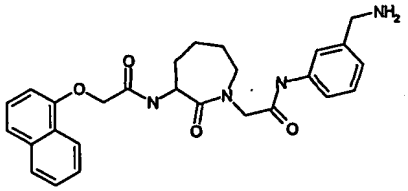
57		559
58		482
59		508
60		471
61		461
62		511

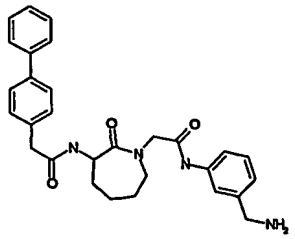
63  544

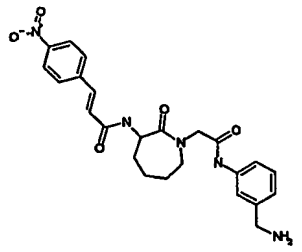
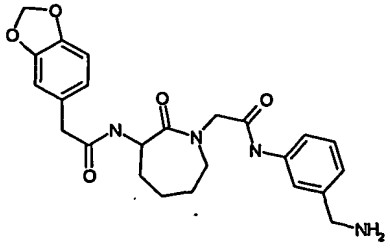
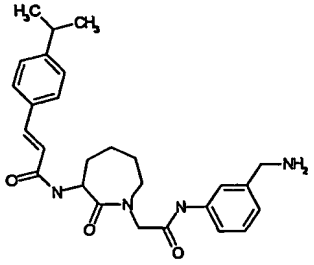
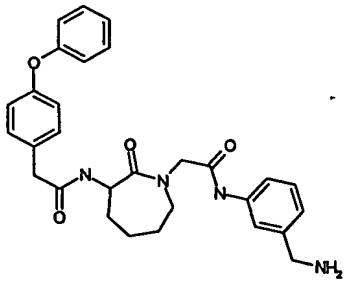
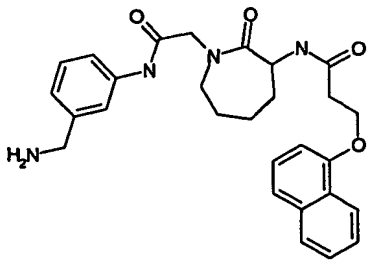
64  497

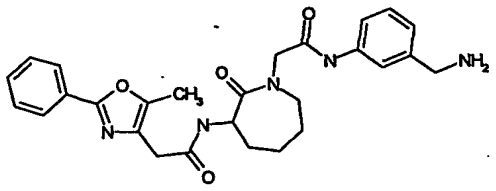
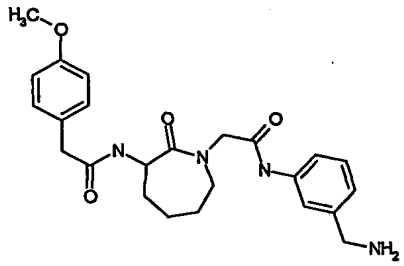
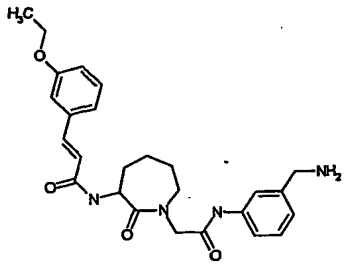
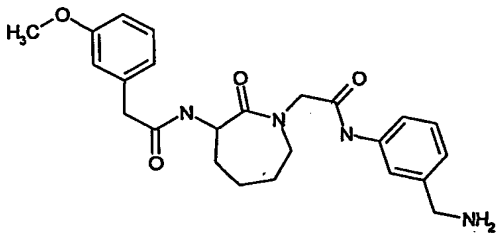
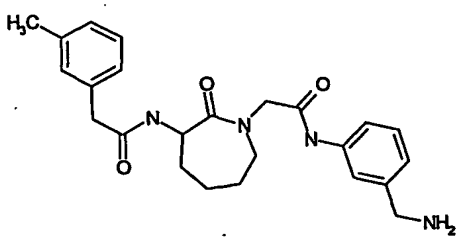
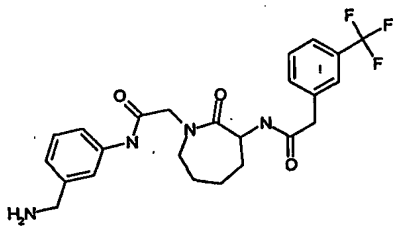
65  522

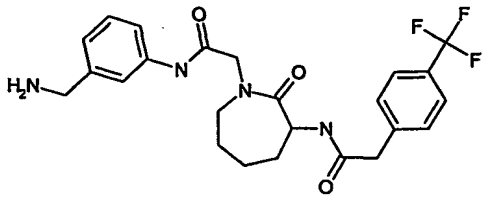
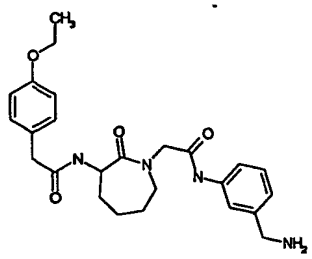
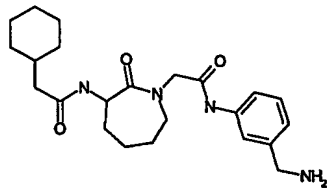
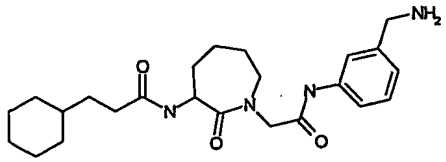
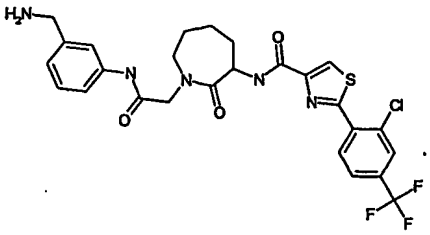
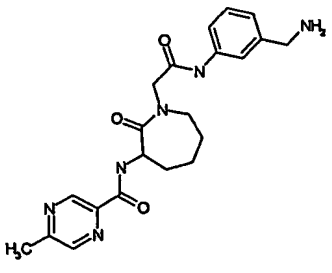
66  514

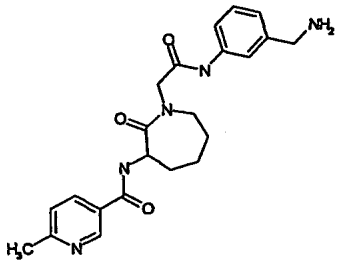
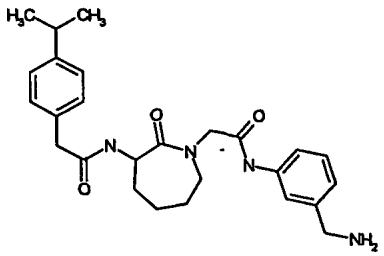
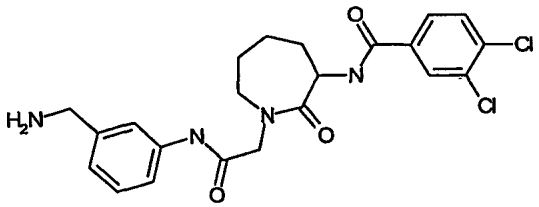
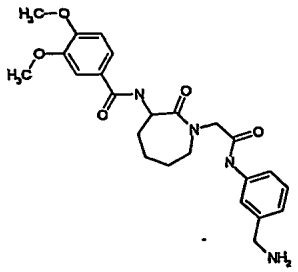
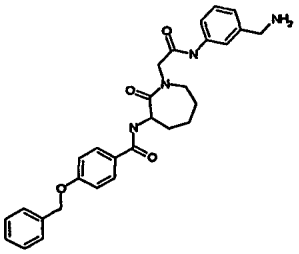
67  475

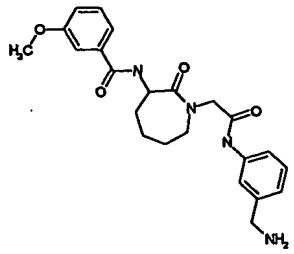
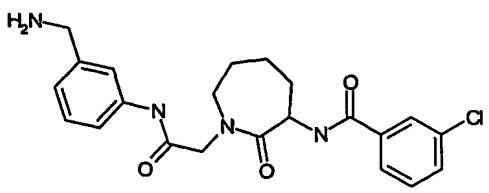
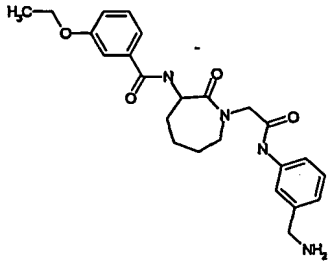
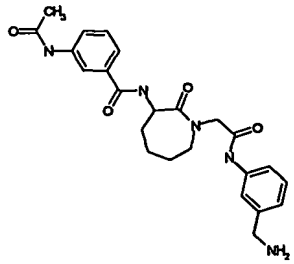
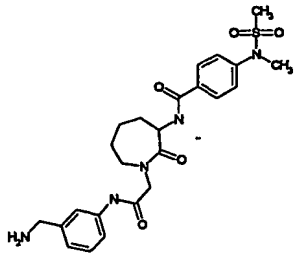
68  485

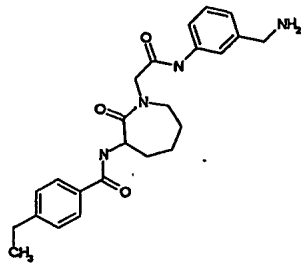
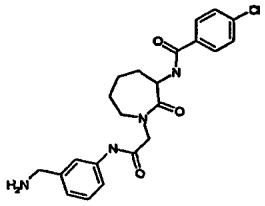
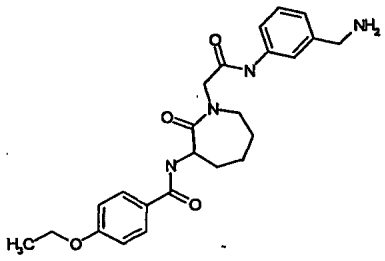
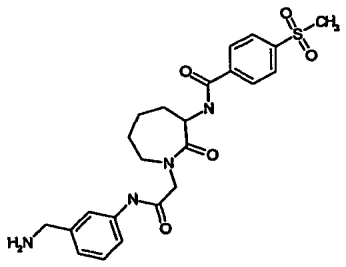
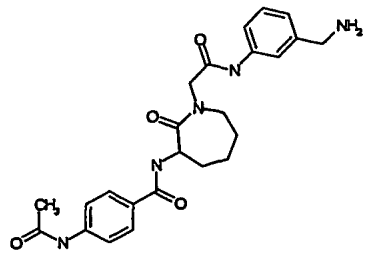
69		466
70		453
71		463
72		501
73		489

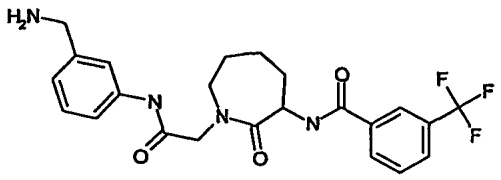
74		490
75		439
76		465
77		439
78		423
79		477

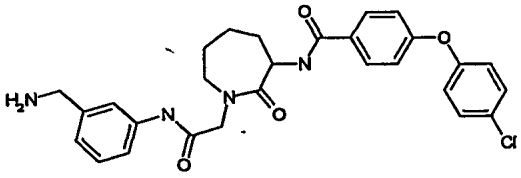
80		477
81		453
82		415
83		429
84		581
85		411

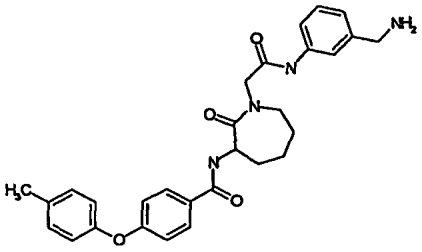
86		410
87		451
88		464
89		455
90		501

91		425
92		429
93		439
94		452
95		502

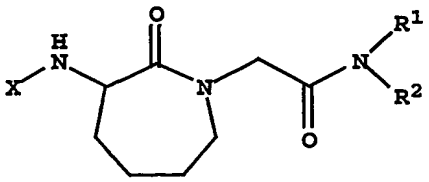
96		423
97		429
98		439
99		473
100		452

101  463

102  522

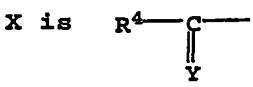
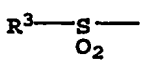
103  501

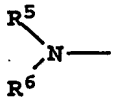
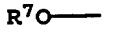
1. A compound having the formula



and a pharmaceutically acceptable salt thereof and all stereoisomers thereof, and prodrug esters thereof, wherein

at least one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aminoalkylaryl, aminocycloalkylalkyl, aminoalkyl, aminoalkylcycloalkyl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, or polycycloalkenylalkyl; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheterolkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, aminoalkyl, alkyloxycarbonylaminoalkyl, arylalkyloxycarbonyl-aminoalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl;

X is  or 

Y is O or S and R^4 is  ,  or R^8

R^3 is selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, or polycycloalkenylalkyl; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl;

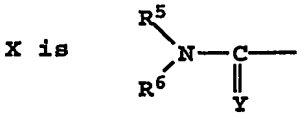
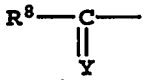
R^5 and R^6 are the same or different and are independently selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, arylcarbonyl, alkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, arylsulfonyl, or alkylsulfonyl, or R^5 and R^6 can be taken with the

nitrogen to which they are attached to form a cycloheteroalkyl ring; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl;

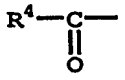
R^7 and R^8 are the same or different and are independently selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl,

arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl.

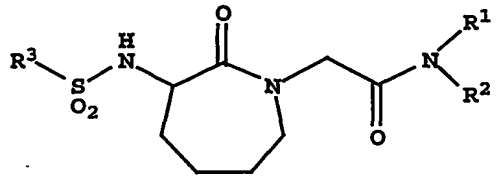
2. The compound as defined in Claim 1 where

(1) X is  or 

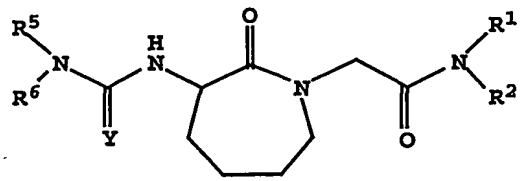
and R^1 and R^2 are independently cycloalkyl, alkenyl, phenyl, benzyl, cyanoalkyl, alkoxycarbonylalkyl, or phenyl mono- or disubstituted with lower alkyl, cyano, hydroxy, dialkylamino, alkoxy, benzyloxy, alkylamino, alkoxycarbonyl, pyrrolidino, morpholino, halogen, alkyl substituted with one or more fluorines, then Y is S; and

(2) where X is  and R^4 is R^8, then R^8 is other than alkyl substituted with hydroxyaminocarbonyl.

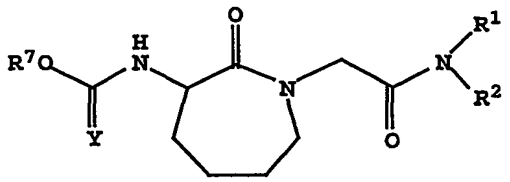
3. The compound as defined in Claim 1 having the formula



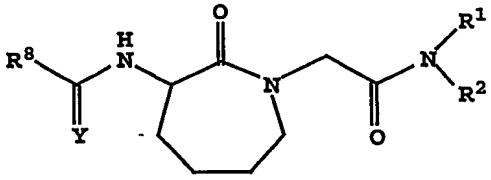
4. The compound as defined in Claim 1 having the formula



5. The compound as defined in Claim 1 having the formula

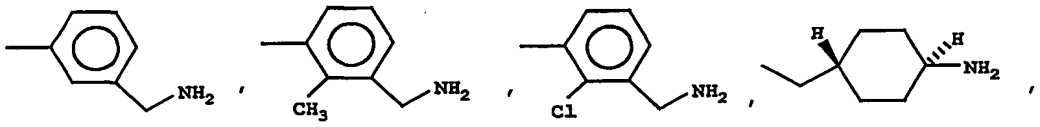


6. The compound as defined in Claim 1 having the formula



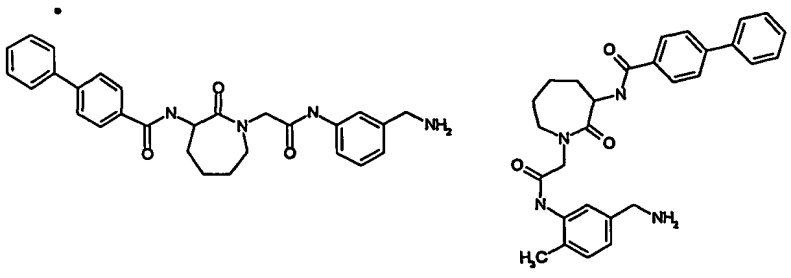
7. The compound as defined in Claim 6 wherein one of R^1 and R^2 is hydrogen and the other is aminoalkylaryl or aminocycloalkylalkyl, and y is O.

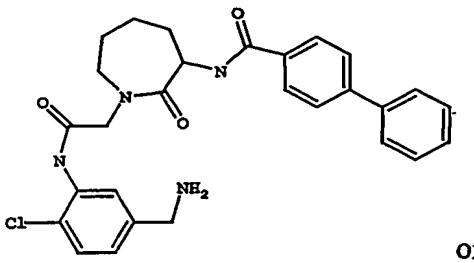
8. The compound as defined in Claim 7 wherein one of R^1 and R^2 is



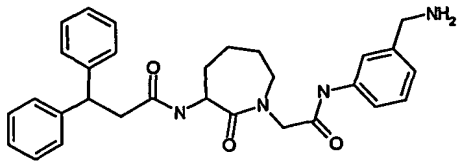
and Y is O.

9. The compound as defined in Claim 1 having the structure

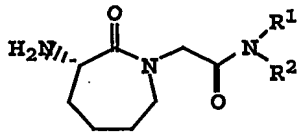




or



10. A compound having the structure



wherein R^1 and R^2 are the same or different and are independently selected from hydrogen, alkynyl, heteroaryl, aminoalkylaryl, aminocycloalkylalkyl, aminoalkyl, aminoalkylcycloalkyl, heteroarylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenyl-alkyl, or R^1 and R^2 can be taken with the nitrogen to which they are attached to form a cycloheteroalkyl ring; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheterolkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, aminoalkyl, alkyloxycarbonylaminoalkyl, arylalkyloxycarbonyl-aminoalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy,

alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfinyl; or a pharmaceutically acceptable salt thereof, with the proviso that at least one of R^1 and R^2 is hydrogen.

11. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

12. Use of a compound as defined in Claim 1 for the preparation of a pharmaceutical composition for inhibiting a serine protease, for treating and/or preventing inflammation, asthma, or allergic rhinitis, for treating and/or preventing medical conditions in a mammalian species related to tryptase, for treating and/or preventing inflammatory bowel disease, psoriasis, conjunctivitis, atopic dermatitis, rheumatoid arthritis, osteoarthritis, chronic inflammatory joint disease, diseases of joint cartilage destruction, treating and/or preventing myocardial infarction, stroke, angina, diabetic retinopathy, diseases involving angiogenesis, tumor growth, cancer, fibrosis, scleroderma, pulmonary fibrosis, liver cirrhosis, myocardial fibrosis, neurofibromas and/or hypetrophic scars.

13. A pharmaceutical combination comprising a compound as defined in Claim 1 in combination with a hypolipidemic agent, a β-adrenergic agonist, an anticholinergic, an anti-inflammatory cortiocosteroid or an anti-inflammatory agent.

14. The pharmaceutical combination as defined in Claim 13 wherein the β-adrenergic agonist is albuterol, terbutaline, formoterol, fenoterol, salmeterol, bitolterol, or pilbuterol, and the anti-inflammatory agent is beclomethasone, triamcinolone, flurisolide, dexamethasone, budesonide, fluticasone, cromolyn, nedocromil, theophylline, zileuton, zafirleukast, monteleukast and pranleukast, and wherein the hypolipodemic agent is pravastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, rosuvastatin or itavastatin.